8

Measles

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Measles is a highly infectious disease transmitted person-to-person by way of the respiratory route; the severity of measles (morbidity, disability, and mortality) is affected by a wide range of epidemiologic, demographic, physiologic, socioeconomic, and behavioral determinants. Almost all children unprotected by immunization will be infected with measles; in the developing world, 1 to 5 percent will die of measles and its complications.

In 1954, Enders and Peebles isolated the measles virus, which paved the way for the development of an effective vaccine. Measles vaccine provides long-term protection to susceptible persons. Use of this vaccine has proved effective in reducing measles cases in both industrial and developing countries. With technical direction and leadership from the World Health Organization's (WHO's) Expanded Programme on Immunization (EPI), advocacy and financial support from the United Nations Children's Fund (UNICEF), and bilateral technical cooperation, national immunization programs have increased the global coverage of measles vaccine for children twelve months of age or younger from 20 percent in 1974 to 78 percent in 1990 (WHO 1991). Although global efforts effectively prevented an estimated 2.12 million measles deaths in 1990, an estimated 880,000 deaths were not prevented. In 1989 the WHO World Health Assembly established measles targets for achievement by the year 1995: a 95 percent reduction in measles mortality, a 90 percent reduction in measles incidence, and a measles vaccine coverage of 90 percent in the first year of life. In this chapter we review what is currently known about measles and its control and identify policies, strategies, and practices that will enable the achievement of the global objectives.

Epidemiology

Measles transmission occurs when an infectious individual comes into close contact with a susceptible individual. The probability that an individual will contract measles in a given time period depends upon his or her immune status (susceptibility to infection), the population size and density of the community, the frequency of the individual's contact with other population members, and the probability that such contacts are with an infectious person. Together, these factors determine not only the likelihood that an individual will be infected but also the age pattern of infection and whether measles is maintained endemically in the population or occurs only in sporadic outbreaks or epidemics.

Susceptibility to Infection

Measles transmission results from the exposure of a susceptible person to respiratory droplets or aerosolized droplet nuclei from a measles-infected person (Black 1982; Bloch and others 1985). The probability that an exposed, susceptible person in a household will be infected by the measles virus is 90 percent or higher.

Most infants are protected from measles at birth by passively acquired transplacental maternal antibodies. Breastfeeding practices affect neither the level nor the persistence of measles antibodies. Studies of 2,917 maternal blood samples from twenty different populations in thirteen countries demonstrated measles antibodies in 99.2 percent of samples (Black 1989), suggesting that a corresponding proportion of newborn infants have some degree of passively acquired antibody immunity. The mean duration of this protection varies considerably, however, ranging from three to six months in some populations to twelve months or more in others. Black identified three factors contributing to these interpopulation differences: (a) "the women of different countries have different amounts of measles antibody to pass to their children"—maternal titers as measured by hemagglutination inhibition in Gazankulu, South Africa, were eightfold higher than those from Taiwan; (b) "there are genetic or environmentally determined differences in the efficiency of the placenta in transporting IgG [immunoglobin G]"—that is, simultaneous collections of maternal and cord blood have shown maternal-infant differences in hemagglutination inhibition titer ranging from +0.86 $\log_2$ in New Haven, Connecticut, to -0.97 $\log_2$ in Kuala Lumpur, Malaysia; and (c) "there are differences in the rate at which children lose passively acquired antibody immunity"—for example, differences in the half-life of maternally acquired antibody (Black 1989, p. 19). These differences may be related to the rate of infection with other infectious agents, leading to

increased catabolism of IgG, and higher rates of diarrhea, leading to increased loss of IgG into the interior lumen of the gut (Black 1989, p. 19). Geographic variations in the age at which infants lose passive immunity, as estimated by serologic studies, are consistent with observed patterns of immunologic response to vaccine or disease on exposure to infection.

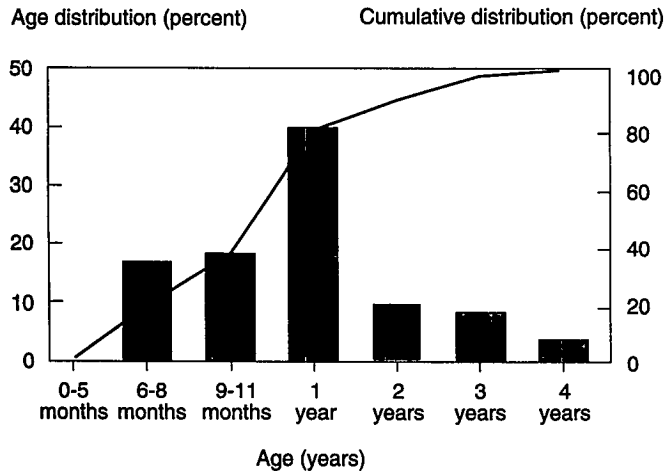
Age of Infection in Four Populations

Individuals exposed to measles virus and not protected by either maternal or vaccine-acquired immunity usually develop infection. Age-specific rates of measles infection are determined by the number of infective measles cases in the population, the size and age composition of the pool of susceptibles, and the rate and age pattern of contact. Widely divergent age patterns of measles transmission are seen in the following four populations: (a) high-density urban populations in developing countries (for example, Kinshasa, Zaire); (b) rural populations in developing countries with low vaccine coverage (for example, Matlab, Bangladesh); (c) rural populations in developing countries with high vaccine coverage (for example, Lesotho); and (d) populations in industrial countries with high vaccine coverage such as the United States of America (figures 8-1–8-4).

HIGH-DENSITY URBAN—IN DEVELOPING COUNTRIES. In large cities in western and central Africa, an urban transmission pattern prevails; measles occurs primarily in the first two years of life. The early age of infection can be attributed to the high population density, the early exposure of infants to infectious individuals as mothers carry their babies on their backs on crowded public transport and in urban markets, and the early loss of maternally acquired antibody in relation to such loss in industrial countries. Measles is endemic in the population and cases occur continuously. Data on 10,078 measles cases from the preimmunization era were collected from the Lagos Infectious Disease Hospital in Nigeria; they showed that 36 percent of hospitalized cases occurred in infants twelve months of age or younger (the median age of infection was fifteen months) and that 85 percent of admissions were of children less than thirty-six months old (Smith and Foster 1970). Moderate levels of vaccine coverage have not always changed this urban pattern of early infection. In Kinshasa, Zaire, where measles vaccine coverage during 1983 in children of twelve through fifty-nine months was 62 percent, a community survey showed high rates of measles transmission in infants and young children as indicated by the following age distribution of cases: six through eight months, 18 percent; nine through eleven months, 19 percent; one year, 40 percent; and two years, 10 percent (figure 8-1) (Taylor and others 1988). An estimated 77 percent of cases occurred prior to age three.

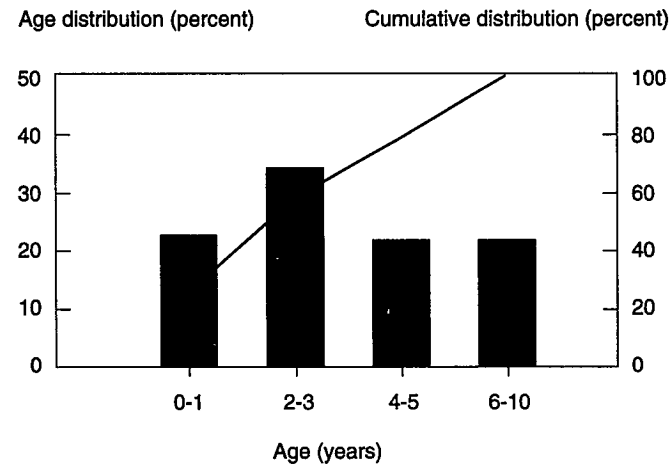
RURAL—IN DEVELOPING COUNTRIES WITH LOW VACCINE COVERAGE. In rural areas, where contact between young, susceptible children and infectious individuals is less frequent than in urban areas, measles is primarily a disease of childhood. Community surveillance data from Matlab, Bangladesh, collected prior to the introduction of measles vaccine, showed 23 percent of cases occurring in children under two years, 34 percent in children two and three years old, 22 percent in children four and five years old, and 22 percent in children six to ten years old (figure 8-2) (Koster and others 1981). Although the population density in Bangladesh is one of the highest in the world, the relative isolation of rural enclaves, the riverine geography, and the limited social mobility of the traditional Moslem culture result in a low probability that the measles virus will be introduced into a village and thus a low probability of exposure

Figure 8-1. Age Distribution of Measles, Kinshasa, Zaire, 1983



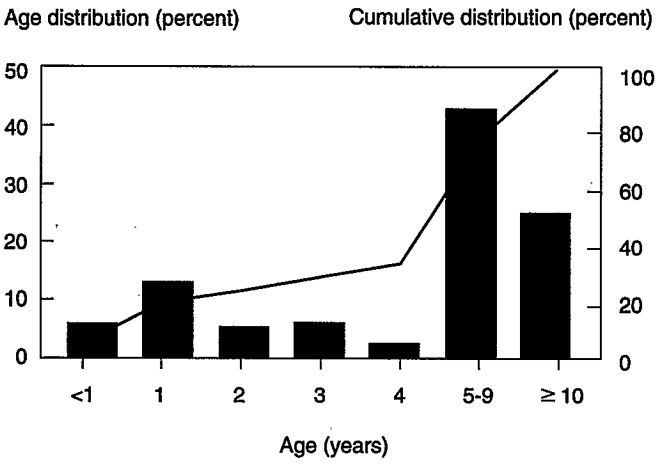
Source: Taylor and others 1988.

Figure 8-2. Age Distribution of Measles, Matlab, Bangladesh, 1975–76



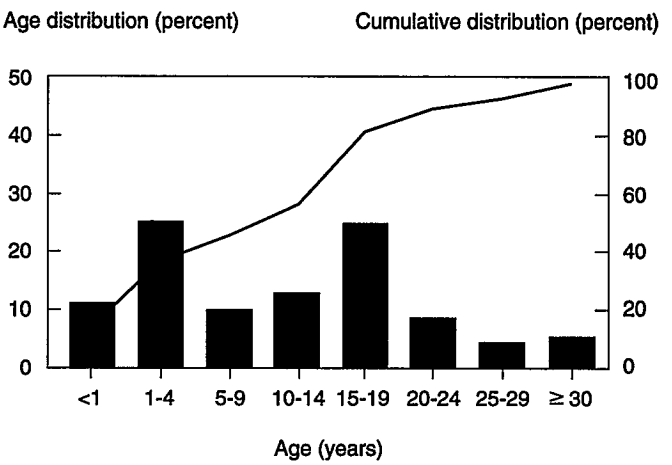
Source: Koster and others 1981.

Figure 8-3. Age Distribution of Measles, Lesotho, 1988



Source: Lesotho 1990.

Figure 8-4. Age Distribution of Measles, United States, 1989



Source: MMWR 1990.

of susceptibles to measles infection. In such areas, measles occurs in sporadic epidemics and vanishes between outbreaks.

RURAL—IN DEVELOPING COUNTRIES WITH HIGH VACCINE COVERAGE. Many developing countries are achieving 80 percent measles immunization during the first year of life, the target established for 1990. In countries with low population density—for example, Lesotho—significant reductions in measles incidence and a corresponding change in the age pattern of disease have been documented. The age at onset of measles has increased; 60 percent of cases occur in children over five years of age (Lesotho 1990) (figure 8-3). This change is not being seen in the more densely populated developing countries with similar levels of vaccine coverage, such as Rwanda, Burundi, and Malawi.

INDUSTRIAL COUNTRIES WITH HIGH VACCINE COVERAGE. In the United States, where, in the prevaccine era, measles was primarily a disease of children, childhood immunization coupled with mandatory school immunization has reduced measles incidence by 98 percent (Markowitz and Orenstein 1990). The national goal of measles elimination has, however, been frustrated by outbreaks affecting urban preschoolers, who are primarily unvaccinated, and high school and college students, who, as a group, are highly vaccinated. The latter outbreaks represent transmission among the 2 to 5 percent who are not protected by a single dose of measles vaccine (United States, National Vaccine Advisory Committee 1991).

Measles Infection and Its Cost

While measles is recognized as an acute childhood infection, the long-term costs in terms of morbidity, disability, and mortality are less well understood.

Clinical Illness

Measles is a clinical illness easily recognized both by health workers and by experienced family members, and it frequently has a distinct name in the local language. The disease has been well described by Preblud and Katz: after an incubation period of ten to twelve days, "the prodromal stage is heralded by the onset of fever, malaise, conjunctivitis, coryza, and tracheobronchitis manifesting as cough, and it lasts for 2–4 days. . . . The temperature rises during the ensuing 4 days and may be as high as 40.6° C. . . . The rash is an erythematous maculopapular eruption that usually appears 14 days after exposure and spreads from the head to the extremities over 3–4 days. Over the next 3–4 days, the rash fades in the order of appearance. Desquamation can be detected in areas of greatest involvement" (Preblud and Katz 1988, p. 183).

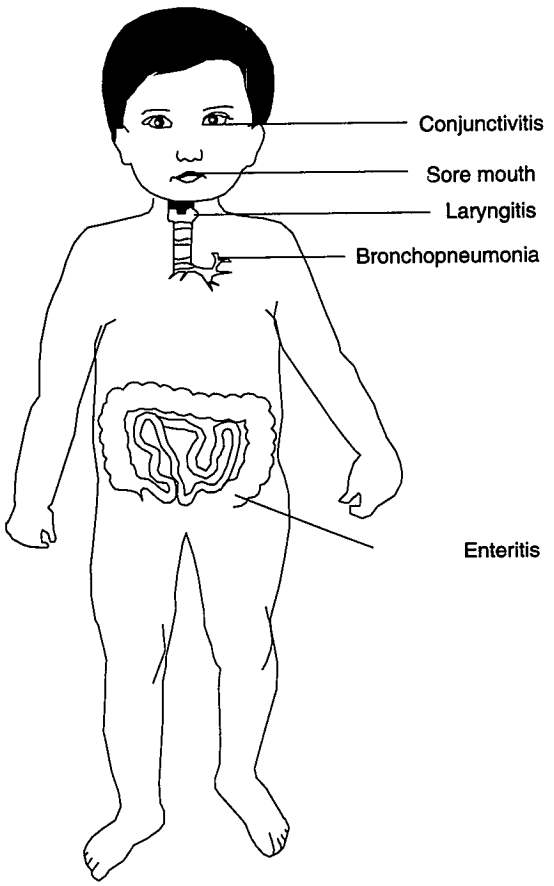
Naturally occurring measles infection provides lifetime protection against reinfection. This was clearly demonstrated in the 1846 outbreak in the Faroe Islands, where infection was limited to those under age sixty-five, individuals born after the last measles epidemic in 1781 (Panum 1939).

In severe disease, a frequent occurrence in developing countries, the manifestations of clinical illness reflect the epithelial loci of infection as illustrated in Morley's classic diagram of severe measles: eyes (conjunctivitis), larynx (laryngitis), lungs (pneumonia), and gastrointestinal tract (diarrhea [Morley 1973, p. 214]; figure 8-5).

Complications

Most measles deaths are attributed to complications, which may be acute (within one month) or delayed (one month to one year). In industrial countries—for example, the United States—the most commonly cited complications are otitis

Figure 8-5. Clinical Manifestations of Severe Measles



Source: Morley 1979.

media (6 percent), diarrhea (6 percent), pneumonia (4 percent), measles encephalitis (0.2 percent), subacute sclerosing encephalitis (1 in 100,000 measles cases), and death (0.1–0.2 percent) (Preblud and Katz 1988; Atkinson and Markowitz 1991). Fifteen percent of the reported cases in the United States required hospitalization.

The distribution of complications in developing countries is somewhat different. Using active surveillance to identify measles cases in the community, investigators of 2,386 cases of measles in Sri Lanka documented complication frequencies as follows: diarrhea, 37 percent; respiratory infections, 30 percent; ear infections, 7 percent; and convulsions 2 percent (WHO/EPI Sri Lanka 1985). Fifty-seven percent of cases had medical care (Bloch, de Silva, and de Sylva 1983).

Morley's classic study from Imesi-Ile, Nigeria, was the first to document the long-term effect of measles on child health in developing countries. In that study, 25 percent of the children with measles lost 10 percent or more of body weight (Morley 1973). The time required to regain that weight ranged from 4.5 weeks for children with no diarrhea to 8.1 weeks for those with diarrhea. Further data on the relation between diarrhea and measles come from Bangladesh, where a large outbreak of measles occurred in twelve villages among 5,775 children undergoing prospective surveillance for nutrition and diarrhea (Koster and others 1981). The frequency and duration of diarrheal episodes increased beginning one week before and lasting four weeks after the onset of rash. Fifty-one percent of the diarrheal episodes lasted longer than seven days compared with 25 percent of the diarrheal episodes of those who did not have measles. The case-fatality rate (CFR) for those with measles who had diarrhea episodes longer than seven days (11.9 percent) was significantly greater than the CFR for those with measles but without diarrhea (4.0 percent). Children with postmeasles diarrhea had a significant and prolonged (10 percent) deficit in weight-for-height. In a WHO-sponsored review assessing potential interventions to reduce diarrhea morbidity and mortality, it was projected that measles immunization could prevent 0.6 to 3.8 percent of all diarrheal episodes and 6 to 26 percent of all diarrheal deaths (Feachem and Koblinsky 1983).

Postmeasles pneumonia is the main cause of measles-associated mortality in the developing countries; 56 percent of measles-associated deaths in a community outbreak in Uttar Pradesh in India and 92.8 percent of measles-associated deaths in a hospital in Ilorin, Nigeria, were attributed to pneumonia (Fagbule and Orifunmishe 1988; Narain and others 1989). In the Sri Lanka community survey (CFR, 1.3 percent), 44 percent of measles-associated mortality was attributed to pneumonia, 25 percent to diarrhea, 19 percent to convulsions, and 9 percent to coma (Bloch, de Silva, and de Sylva 1983). Measles is responsible for a significant proportion of acute respiratory morbidity and mortality, 6 to 21 percent of the morbidity and 8 to 93 percent of the mortality (Markowitz and Nieburg 1991).

Studies have documented transient post-measles immunosuppression (Whittle and others 1973; Dossetor, Whittle, and Greenwood 1977; Kaschula, Druker, and Kipps 1983). Hussey and Simpson (1991) have identified immunosuppression as a probable cause of increased risk of nosocomial bacteremia in measles cases (3.37 per 100 hospital admissions), as compared with nonmeasles pediatric admissions (0.57 per 100 admissions). General immunosuppression following measles is an important factor in measles-associated mortality. Autopsy studies, which revealed serious nonbacterial bronchiolar and interstitial necrosis caused by adenovirus, measles virus, and herpes virus, indicate a failure of the immune mechanism in the postmeasles child (Kipps and Kaschula 1976).

The main causes of long-term disability following measles have been identified as blindness and malnutrition. In Africa, where the prevalence of blindness in preschool children is estimated at 1 in 1,000, measles has been identified as responsible for half of childhood blindness (Foster and Johnson 1988).

Mortality

In some developing countries, measles CFRs are 300 times those currently reported in industrial countries. Such rates were

common in Europe in the 1800s. In the well-documented outbreak in Sunderland, England, in 1885, 25 of 311 measles patients died, a CFR of 8 percent (Drinkwater 1885). Community studies of measles outbreaks between 1961 and 1978 show CFRs from 1.5 to 15 percent (Walsh 1983; Cutts 1990; Cutts and others 1991). High mortality from measles was initially thought to occur only in Africa, but high CFRs from measles have also been reported in Asia and Latin America, for example, 7 percent in Tamil Nadu, 5.7 percent in Uttar Pradesh, and 4.5 percent in Guatemala (Gordon 1965; John and others 1980; Narain and others 1989).

Although measles outbreaks that result in high mortality are more likely to be investigated and reported, data from prospective surveillance among populations that have been studied in developing countries have also revealed high measles CFRs: 6.5 percent in Kenya; 6.1 percent in Zaire; 6.5 percent in Senegal; and 3.7 percent in Bangladesh (Voorhoeve and others 1977; Kasongo Project Team 1981; Koster and others 1981; Garenne and Aaby 1990). The World Health Organization estimates that 880,000 measles deaths occurred in 1990 (WHO 1991).

Mortality Risk Factors

High infant and child mortality in the developing world is usually attributed to the complex interaction of poverty, undernutrition, and infection. Mosley and Chen have proposed a child mortality proximate determinant model which emphasizes the importance of the complex interactions of maternal behavior, environmental contamination, nutritional deficiency, injury, and personal illness control action including preventive measures and seeking treatment at time of illness (Mosley and Chen 1984). Epidemiologic studies have documented a number of risk factors which explain, in part, the high rates of measles-associated mortality in the developing world.

AGE. Case-fatality rates exhibit substantial variations by age, the higher CFRs occurring in the younger age groups, usually six to eighteen months of age. The age pattern of mortality varies in different populations, reflecting both the epidemiology of the disease and the general health environment in which the child exists. In a recent outbreak in Rwanda, reported age-specific CFRs decreased with age: zero through eight months (3.0 percent); nine months through twenty-three months (1.4 percent); twenty-four months through fifty-nine months (1.0 percent); and sixty months and older (0.5 percent) (Weierbach 1989). In contrast, the Kasongo study from Zaire documented the highest rates in children of thirteen months to twenty-four months: one month to six months, 0 percent; seven months to twelve months, 6.2 percent; thirteen months to twenty-four months, 9.8 percent; twenty-five months to thirty-six months, 4.3 percent; and thirty-seven months to sixty months, 2.8 percent (Kasongo Project Team 1981). Data from Bangladesh show similar CFRs from measles in all age groups: one month to twenty-three months, 4.4 percent; twenty-four months to forty-seven months, 4.2 percent; and forty-eight months to seventy-one months, 4.2 percent (Koster and others 1981).

GENDER. In two studies from Asia, CFRs were higher for females than for males. In Bangladesh, the CFR among males (0.98 percent) was significantly less than for females (2.64 percent) (Bhuiya and others 1987). Similar results were reported from Varanasi in India: 1.3 percent for males and 3.3 percent for females (Chand and others 1989). Such differences have not been documented in African studies, suggesting that differences arise from sex-specific patterns of child care and response to illness rather than to biological differences between the sexes.

SOCIOECONOMIC STATUS. Using a multivariate logistic regression analysis of community data collected in the Matlab Bangladesh field area, Bhuiya and others (1987) identified low number of household articles owned (a proxy indicator of poverty) as a significant risk factor for measles mortality.

INTENSITY OF EXPOSURE: ACQUISITION OF MEASLES IN THE HOME. Aaby, in his studies in Guinea-Bissau, documented increased rates of measles mortality in secondary cases acquired in the home (Aaby 1988). Reexamination of the Machakos data from Kenya and ORSTOM data from Senegal has shown similar findings (Aaby and Leeuwenburg 1988; Garenne and Aaby 1990). In the Senegal data, odds ratios (OR) on mortality risk were related to the probable intensity of exposure: same hut (OR 3.8, 95 percent confidence interval CI, 1.7–8.4), same household (OR 2.3, 95 percent [CI], 1.0–5.7), and same compound (OR 1.9, 95 percent CI, 0.6–6.0).

NUTRITIONAL STATUS. Although high mortality from measles is seen in undernourished populations, individual nutritional status has not proved to be a reliable predictor of mortality in most studies (Aaby 1988; Koster and others 1981). During the last decade, vitamin A deficiency has been increasingly linked to higher child mortality and to high measles-associated mortality (Sommer 1990). In Tanzania, a clinical trial showed decreased measles mortality in hospitalized patients who received vitamin A (Barclay, Foster, and Sommer 1987). In Zaire, a multivariate logistic regression model of 283 measles patients admitted to two Kinshasa hospitals identified an increased mortality risk in children less than two years of age with a vitamin A level of less than 5 micrograms per deciliter (relative risk [RR] 2.9—CI 1.3–6.8 [Markowitz and others 1989]). In South Africa, a randomized double-blind trial using vitamin A in the treatment of 189 measles cases reduced measles mortality by half; the durations of pneumonia, diarrhea, croup, and hospitalization were shortened (Hussey and Klein 1990). Of historical note is Hussey's reference to a preantibiotic-era paper by Ellison (1932), in which intensive vitamin therapy reduced measles CFR from 8.7 percent to 3.7 percent and measles pneumonia CFR from 67.7 percent to 31.3 percent. Measles and its sequelae have also been identified as signif-

icant risk factors contributing to the development of protein-calorie malnutrition and kwashiorkor.

ABSENT OR DELAYED MEDICAL CARE. Most of the mortality associated with measles can be prevented through timely and appropriate medical care. In Senegal, early treatment of measles has resulted in the near elimination of measles mortality (Garenne and others 1992). Timely appropriate case management is rare in many developing countries because of lack of access to care, delayed seeking of care, lack of trained personnel, or lack of appropriate drugs. Contact with health facilities usually occurs late in the illness. In a hospital-based study from Burkina Faso, 55 percent of measles deaths occurred within twenty-four hours of admission (Sahuguede and others 1989). The symptoms upon admission to the hospital of 714 measles patients illustrate the seriousness of illness at the time of entry into the hospital: dehydration (91 percent), diarrhea (64 percent), conjunctivitis (56 percent), fever above 39.5° C (50 percent), respiratory infection (46 percent), and cardiovascular collapse (34.5 percent).

LOCAL TREATMENT. In many traditional cultures, measles is considered a normal event. In others, it has been attributed to the work of witches or sorcerers (Imperato and Traore 1969). Withholding food, especially protein, and fluids from measles cases has been reported (Morley 1973). In the Machakos data, measles was identified among "God's diseases" (Maina-Ahlberg 1979). Withholding of water and milk from children sick with measles was documented in 62 percent of 242 cases. Of cases reported, 50 percent received indigenous medicines and 98 percent also received Western medicine. Local treatments, restriction of fluids and food, delay in access to effective chemotherapy, and use of potential toxic substances have been identified as potential contributors to increased measles-associated mortality.

NONVACCINATION. The single most important determinant of measles morbidity and mortality is vaccination status. Almost all children unprotected by measles vaccine will eventually be infected with measles and 1 to 5 percent will die.

Economic Cost

The economic cost of a disease can be divided into direct and indirect costs. Direct costs are those borne by the health system in the prevention and treatment of the disease and by households or individuals in seeking preventive services or treatment. Indirect costs are usually measured in terms of lost productivity of workers as a result of their premature death or disability.

Few estimates of the costs for treatment of measles have been made in developing countries. Because care is generally delayed or absent, reliable data on costs of treatment for measles cases is not routinely available. In a study in Mexico, Cardenas-Ayala and others (1989) estimated the costs of medical care (hospitalization, physician's visits, medical treatment, and rehabilitation) for measles patients; they also estimated the number of deaths that would have occurred in the absence of a measles immunization program. The analysis demonstrated large societal benefits of measles immunization with a benefit-to-cost ratio of 100 to 1. Indirect costs were estimated to be approximately 77 times the direct costs, but the authors acknowledge that the direct-cost measure represents a very low level of access to care and a severe underreporting of measles cases. A previous study (Verduzco, Calderon, and Velazquez-Franco 1974) of measles immunization in Mexico calculated a benefit-to-cost ratio of 27 to 1, although indirect costs (as measured by lost earnings) were not estimated.

Estimates of both direct and indirect costs attributable to measles were made in a study comparing Israel, the West Bank, and Gaza (Ginsberg and Tulchinsky 1990). Total costs for patients with simple cases of measles, patients requiring hospitalization, and patients with complications were estimated in each of the three regions. Estimates for a simple case of measles (treated in the outpatient setting) ranged from $13 in Gaza to $141 in Israel.[1] Costs of early mortality due to measles ranged from $11,628 in Gaza to $76,518 in Israel. The wide range in the latter estimates highlights one of the most difficult methodological issues in making estimates of premature mortality—that of placing a monetary value on life. Any of the available methods relates valuation of life to social productivity and is usually measured in discounted future expected earnings. Thus, the value of a life in Gaza, a region with low earnings and income, is valued below a life in Israel, an area with higher per capita income.

The economic cost of measles in industrial countries has been measured in more detail. Using 1983 data in the United States, White, Koplan, and Orenstein (1985) estimated a benefit-to-cost ratio for measles immunization of 11.9 to 1. Both direct and indirect costs were estimated with and without a vaccination program. Indirect costs were 3.2 times direct costs. The cost per measles case was estimated to be $209 (in 1983 dollars). Cost-benefit studies of measles immunization have consistently demonstrated large social benefits (Mast and others 1990) because of the high direct cost of treating complications of measles cases, the attendant indirect costs of work and productivity loss, and the relatively low cost of immunization programs.

The economic burden of measles can also be measured by days of healthy life lost as a result of premature mortality and disability. In Mali (Duflo and others 1986), measles ranked fifth among diseases in terms of days of healthy life lost, with 94.7 percent of the days lost because of premature death (as opposed to illness or disability). Losses resulting from measles accounted for 6.4 percent of the total days of healthy life lost in Mali. An earlier study in Ghana (Ghana Health Assessment Project Team 1981) ranked measles second, accounting for 7.3 percent of the total days of healthy life lost in the population.

Barnum (1989) notes the importance of applying a discount factor in order to account for the fact that the number of healthy life-years lost which are attributed to a disease each year do not actually occur in that year. The choice of discount

factor is thus critically important when ranking diseases by productive life lost. Using the Ghana data, Barnum shows that the relative ranking of measles among diseases is second when the discount rate is zero but is fifteenth when the discount rate is 0.20. When the discount rate is zero, the diseases with the greatest cost in lost productivity are the diseases of childhood, such as measles, but as the discount rate rises, adult problems increase in importance and childhood diseases fall in significance.

Prevention of Measles

Measles can be prevented through immunization of the susceptible child with a potent live virus vaccine.

Vaccine

The history, uses, and effectiveness of measles vaccines are discussed below.

HISTORY. Measles virus was first isolated in the 1950s by Enders and Peebles (1954) from a child infected with measles and was attenuated through passage in tissue culture. Most of the vaccine strains used today (Schwarz, Moraten, Beckenham, Edmonston-Zagreb, EKC, and AIK-C) were developed from the original Edmonston isolation (Preblud and Katz 1988). The Leningrad-16 strain used in the former U.S.S.R. and eastern Europe, the strains used in China, and the CAM-70 strain were derived independently of the Edmonston isolation (Clements and others 1988). Heat stability of most strains has been increased through the addition of stabilizers. The minimum recommended dose of current standard measles vaccine applied at or after the age of nine months is 1,000 median tissue culture infective dose given subcutaneously in the arm.

AGE OF IMMUNIZATION. Because of differences in the duration of protection from passive maternal protection and differences in risk of exposure, selection of the age of immunization requires a balancing of two factors: "the earliest age at which high rates of seroconversion can be obtained, and the age group with the greatest risk of infection" (Orenstein and others 1986). On the basis of epidemiologic data on age-specific measles incidence and age-specific seroconversion data, WHO has recommended nine months as the optimal age for measles immunization in most developing countries (Kenyan Ministry of Health and WHO 1977; WHO/EPI Kenya 1979). In Haiti, seroconversion to a standard dose of Schwarz vaccine ranged from 45 percent in six-month-old children to 100 percent in children at twelve months of age (Halsey and others 1985). In some industrial countries, 100 percent seroconversion is not obtained until children are fifteen months of age. In the United States, policy recommendations regarding age for measles immunization have changed three times in response to field data on vaccine efficacy. Measles immunization was initially introduced in children at nine months of age. When challenge with wild virus identified vaccine failures in children vaccinated at nine to eleven months and subsequently in those vaccinated at twelve to fourteen months, the minimum age of immunization was increased to twelve months in 1965 and then to fifteen months in 1976 (Orenstein and others 1986). In 1989, a two-dose measles vaccine schedule was recommended (ACIP 1989). The United States experience emphasizes the importance of epidemiology, disease surveillance, and outbreak investigation in setting and amending national vaccine policies.

In Lesotho, where the age for measles immunization is nine months and coverage has reached 80 percent, 60 percent of cases occur in school-age children. Serologic studies using enzyme-linked immunosorbent assay have documented 13.6 percent seronegativity in six- and seven-year-old children entering school (Lesotho 1990). When a policy of vaccinating all schoolchildren for the first time, regardless of vaccine history, proved difficult to maintain, a second dose of measles vaccine was added to the routine scheduled booster dose of the diphtheria-pertussis-tetanus (DPT) at fifteen months.

Immunization with potent vaccine administered at the recommended age does not ensure seroconversion or protection. Primary vaccine failures (the lack of a serologic and immunologic response to initial immunization) do occur. Secondary vaccine failures (the occurrence of disease in previously successfully immunized children) have been reported but are thought to be rare. In a vaccine study population in British Columbia, 93 percent of 188 children responded serologically to immunization. This percentage corresponds to a primary vaccine failure rate of 7 percent. In 1985–86 an outbreak of measles occurred in the same British Columbia study population; 9 of the 175 original seroconverters developed measles, corresponding to a secondary vaccine failure rate of 5 percent (Mathias and others 1989). Low rates (2 to 5 percent) of secondary vaccine failure have also been documented by other authors (Edmonson and others 1990; Markowitz, Preblud, Fine, and Orenstein 1990).

VACCINE EFFICACY. Orenstein and colleagues (1985) have outlined a range of methods for the field evaluation of vaccine efficacy (VE), including screening methods that can be used at health facilities, outbreak investigations, and case control studies. Several factors limit vaccine efficacy. They include the following:

- Interference with vaccine virus replication by prenatally acquired maternal antibody
- Exposure to wild virus infection prior to the recommended or actual time of immunization
- Impotent vaccine resulting from failure of the cold chain (the system designed to ensure vaccine potency from site of manufacture, through shipment, to central storage, to distribution, to peripheral storage, to dilution with cold diluent, to vaccine delivery)
- Incorrect administration of measles vaccine, for example, administration of less than the required 0.5 cubic centimeters or immunization at an inappropriate age

- Failure of immunologic response of a susceptible person to potent vaccine for unknown reasons

In industrial countries, vaccine efficacy in children vaccinated at twelve months to fifteen months of age is high. In Poland, measles vaccine efficacy has been estimated at 97 percent (WHO/EPI Poland 1986). In a measles outbreak investigated in Browning, Montana, vaccine efficacy was estimated at 96.9 percent (95 percent CI 89.5–98.2) (Davis and others 1987). Evidence to date indicates that live virus measles immunization also induces life-long immunity in most individuals (Markowitz, Preblud, Fine, and Orenstein 1990). In developing countries, where logistics and maintenance of the cold chain are difficult, seroconversion studies have occasionally documented low rates of seroconversion: 40 percent in Yaoundé, Cameroon, and 0 percent in Guinea-Bissau (McBean and others 1976; Aaby and others 1989). Most outbreak investigations in developing countries, however, document rates of vaccine efficacy in the range of 70 to 90 percent. Examples include community and hospital studies of urban measles in Point Noire, Congo, which reported vaccine efficacies of 78 percent and 87 percent, respectively; a Tanzanian case-control study in which card-documented records revealed a vaccine efficacy of 96 percent (95 percent confidence level 83–99 percent); and a recent study in rural Burundi that reported a vaccine efficacy of 72.4 percent (Dabis and others 1988; Chen 1990; Killewo and others 1991). Even under good cold-chain conditions, vaccine efficacy in developing countries is lower than in industrial countries because vaccine is applied at an age when 10 to 20 percent of children still have maternal antibody. Because of the risk of infection at an early age, vaccination cannot be delayed.

COST-EFFECTIVENESS: EPI. Total costs of the Expanded Programme on Immunization have been estimated in a number of countries (Brenzel 1990, 1991). Although the range is quite wide, the average cost of approximately $15.00 per fully immunized child (BCG vaccine, oral polio vaccine [OPV; four times], DPT [three times], and measles) appears to be indicative of true program costs. Comparisons of the cost per fully immunized child for alternative immunization strategies are approximately $11.00 for facility-based programs, $10.60 for mobile programs, and $15.60 for accelerated strategies.

Several crucial questions remain regarding the cost of immunization programs, including the relationship of costs to coverage, the effect of technology on costs, the current cost levels and the ability of countries to meet stated immunization targets (Rosenthal 1990), the distribution of costs between countries and donor groups, and the relative costs of alternative immunization strategies (for example, campaigns) and sustainable increases in coverage. Furthermore, all the EPI cost studies have been at one point in time; they have not been conducted in conjunction with coverage surveys over time. It is thus difficult to predict changes in cost per fully immunized child as coverage increases. The 1995 targets established by WHO and endorsed at the 1990 World Summit for Children (90 percent reduction in measles morbidity and 95 percent reduction in measles mortality) were estimated for the Task Force on Child Survival at $15 per child for up to 80 percent coverage and then an additional $1 for each 1 percent increase in coverage up to $30 for 95 percent coverage (Forgy and others 1990). The authors of two studies conducted in Swaziland five years apart, 1984 and 1989, calculated a cost per fully immunized child of approximately $55 for coverage rates of 70 percent and 71 percent, respectively (Robertson 1985; McFarland and Kraushaar 1990). Although the costs are high in relation to other countries, they reflect the tradeoffs of achieving high coverage rates in a small population (approximately 700,000) with excellent access to health services and extensive surveillance and outbreak control activities. The Swaziland studies emphasize the importance of understanding the context in which health services are delivered and the fallacy of applying average cost figures for across all countries and all settings.

The cost of the measles component of the EPI total cost can be determined either as an incremental cost to the total or as the cost base of EPI to which other antigens are added. Using the first method, Phillips, Feachem, and Mills (1987) calculated the incremental cost of adding measles immunization to an existing EPI program as $1.35 (in 1982 dollars). Shepherd, Sanoh, and Coffi (1986) used the second method in Côte d'Ivoire, allocating 75 percent of EPI costs to the measles component. The cost per child vaccinated against measles was $12.30 (in 1980 dollars). The authors of an earlier study in Zambia, using slightly different methods, derived a cost of $8.00 to $14.00 (in 1982 dollars) per child vaccinated against measles in the rural areas and $2.00 to $5.00 in urban areas (Ponninghaus 1980). When estimating the cost of achieving the 1995 measles targets, Forgy and others (1990) attributed the entire cost of EPI ($15.00 per vaccinated child) to the measles component. Those who used UNICEF mortality figures estimated total worldwide costs for achieving the targets to be $5.707 billion; those who used World Bank mortality estimates arrived at a total worldwide cost of $8.517 billion.

Besides variation in methods used to assign costs to the measles component of EPI, several factors influence cost estimates, including the level of immunization activity (volume), the ratio of fixed costs to variable costs, prices of key inputs, the type of technology used, and the productivity of personnel providing services (Brenzel and Claquin 1991). Understanding cost behavior can assist program managers and donor agencies in controlling these factors and thus influencing the costs of measles immunizations.

Most cost studies of EPI and measles immunization focus on the direct cost to the system of providing the service rather than the cost to the family or household in seeking immunization services. Thus, cost figures routinely underestimate the full societal cost of an immunization program.

Given the range of cost and effectiveness estimates, it is not surprising that cost-effectiveness measures of measles immuni-

zation vary considerably. Several studies have attempted to measure cost-effectiveness of measles immunization by the number of measles cases prevented and measles deaths prevented. These estimates are compared in table 8-1.

Since measles contributes to morbidity and mortality from diarrhea, the same measures of cost-effectiveness can be calculated for diarrheal cases and deaths prevented as a result of measles immunization. Phillips, Feachem, and Mills (1987) estimate the cost per diarrheal case prevented at $7 (in 1982 dollars) and the cost per diarrheal death prevented at $143. Another measure of the cost-effectiveness of different diseases and interventions is the number of disability-adjusted life-years (DALYs) added for each intervention. Using data from Côte d'Ivoire and Zambia, Prescott, Prost, and Le Berre (1984) compared the cost-effectiveness of measles immunization with an onchocerciasis program in Upper Volta (now Burkina Faso) with regard to disability-adjusted life-years added. For measles immunization, the cost per DALY is $49 (in 1977 dollars) in Côte d'Ivoire and $56 in Zambia, compared with $150 for the onchocerciasis program.

Great care should be exercised in interpreting and extending the results of cost-effectiveness studies. As Brenzel and Claquin (1991) note, the most cost-effective intervention is not necessarily the most efficient; future costs of programs should cautiously be projected from cost-effectiveness studies because average costs do not remain the same over time; and overall cost savings do not necessarily accrue when the most cost-effective interventions are implemented, because resource allocation decisions are not made solely on the basis of cost-effectiveness results. Findings from cost-effectiveness studies are but one type of information for decisionmaking and must be weighed alongside political, ethical, organizational, managerial, and other factors.

Immunization programs have been the subject of many cost-effectiveness analyses, perhaps because of the large donor investment in such programs and because of the relatively straightforward measure of effectiveness employed. But immunization programs and other preventive interventions should not be subject to a standard which exceeds that of other services, in particular treatment and curative services. When cost-effectiveness analysis is employed, it should be applied to the whole range of services and interventions available in order to obtain a fairer assessment of how all resources are used and how such resources might be more effectively allocated.

Table 8-1. Costs per Measles Case and Death Prevented
(1980 U.S. dollars)

Country	*Case prevented*	*Death prevented*
The Gambia	1.96	41
Côte d'Ivoire	14.00	480
Cameroon	3.30	30–60

Source: Makinen 1980; Shepherd, Sanoh, and Coffi 1986; Robertson and others 1987.

EFFECT ON CHILD SURVIVAL. In 1981, *Lancet* published an article on measles in Zaire which questioned the effect of measles immunization on child survival: "In a zone with high measles case-fatality, the risk of dying between the ages of 7 and 35 months for a vaccinated population was compared with an unvaccinated control group. Life-table analysis for both groups showed that measles vaccination reduced the risk of dying at the age of maximum exposure to measles. The gain in survival probability, however, tended to diminish afterwards to approach that of the unvaccinated group" (Kasongo Project Team 1981, p. 33).

Although the interpretation of these data was questioned (Aaby and others 1981), the issue of replacement mortality has not, until recently, been adequately addressed. Several recent studies, however, have assessed the effect of measles immunization on child survival.

Because a definitive double-blind placebo control study would not be ethical, a variety of methods have been used in the following epidemiologic analyses to assess the effect of measles vaccine on child survival. In developing countries with high mortality in children under five, measles vaccine increases child survival.

- Bangladesh: Using a case-control methodology, Clemens and others matched 536 deaths of children ten to sixty months of age with two age and gender matched neighborhood controls. Measles immunization was associated with a 36 percent (95 percent CI 21–48 percent) proportionate reduction in overall mortality rate. For deaths plausibly associated with measles (measles, pneumonia, diarrhea, and malnutrition), vaccine effectiveness was estimated at 57 percent.
- Bangladesh: Using a cohort methodology and the same population described above, but with an additional year of follow-up, Koenig and others (1990) matched 8,135 vaccinated-unvaccinated pairs by month and year of birth. The mortality rate for the immunized children was 45 percent less than that of the controls ($P < .0001$, Gehan-Wilcoxon test $X^2 = 4.18$). Differences were significant for all children immunized under three years of age.
- Guinea-Bissau: Aaby and others (1989) found that, in a population in which serological data identified a subgroup of children not responding to measles vaccine, subsequent mortality among responders to vaccine (4.8 percent) was significantly less than among nonresponders (13.2 percent), a threefold difference in mortality.
- Haiti: Using a logistic regression model, Holt and colleagues (1990) followed up 1,381 children vaccinated to measure seroconversion rates; two and one half years later, infants who were seronegative at the time of vaccination had significantly lower mortality (1.27 percent) than that of nonvaccinated infants (6.62 percent). The adjusted odds ratio in a multivariate stepwise logistic regression associating measles vaccine with survival was 6.5 (95 percent CI 1.6–27.1). Estimates of measles vaccine effectiveness in prevention of mortality in children from nine months to

thirty-nine months of age ranged from 84.7 percent to 90 percent.

- Senegal: Data from the Khombole study area in Senegal (Garenne and Cantrelle 1986) showed that children six to thirty-six months of age who had been immunized against measles had an overall mortality risk 31 percent lower than nonimmunized controls ($P = .028$).

These data strongly suggest that the survival benefit of measles vaccine is significantly greater than that predicted by measles-specific mortality. Longitudinal data from the Medical Research Council in the Gambia suggest a modest effect on infant mortality but a more marked effect on child mortality when compared with preimmunization data from an adjoining area (Greenwood and others 1987).

The importance of measles in decreasing child survival can also be estimated from retrospective (verbal autopsy) studies of child mortality by cause. Such studies have been used to assess the relative contribution of measles to overall mortality. Using the criteria of age greater than 120 days and rash with fever for at least 3 days, Kalter and others (1990) estimated sensitivity and specificity of a diagnosis of measles as cause of death at 98 percent and 90 percent, respectively. In Sri Lanka, in an analysis of reported deaths among children six months to thirteen years, it was estimated that measles or a measles complication was associated with 53 percent of 122 deaths (WHO/EPI Sri Lanka 1985). In Rangoon, Burma, verbal autopsy follow-up reports of 249 deaths of children age six months to ten years, identified from death certificates, attributed 35 percent of the deaths to measles and its complications (WHO/EPI Burma 1985). Reported causes of mortality attributed to measles included pneumonia, chronic diarrhea, and malnutrition. In a prospective study in Senegal during a period of eight years, measles accounted for 31 percent of deaths of children six months to nine years of age (Pison and Bonneuil 1988).

ALTERNATIVE MEASLES VACCINES. Seroconversion rates to the standard Schwarz strain are low when it is administered prior to nine months of age, and the risk of measles infection is great in high-density areas, where as many as 30 percent of reported measles cases may occur prior to the age of nine months. Because of these factors, improved measles control in areas of high population density requires a vaccine which can be effectively administered before the earliest age of infection, four months to six months. Studies in Mexico by Sabin and others (1983), who used the human diploid Edmonston-Zagreb (EZ) vaccine strain, showed that administration of this vaccine could produce seroconversion in the presence of maternal antibody. Field trials in the Gambia, Guinea-Bissau, Mexico, and Haiti have documented the effectiveness of high-titer EZ vaccine when administered at six months and, in some cases, four months of age (Whittle and others 1984; Aaby and others 1988; Markowitz and others 1990; Job and others 1991). In 1989 the WHO/EPI Global Advisory Group recommended the introduction of high-titer EZ vaccine in areas where measles is a significant cause of mortality in the first year of life (WHO/EPI 1989b). Lack of availability of large quantities of the vaccine has limited the implementation of the WHO recommendation. In Senegal, prospective follow-up of children immunized with high-titer EZ and Schwarz vaccines has shown increased child mortality (Garenne and others 1991). Increased mortality after immunization with high-titer vaccines has also been reported from Guinea-Bissau and Haiti (WHO, personal communication, June 1992). The World Health Organization no longer recommends use of high-titer EZ vaccine (WHO/EPI 1992). Although there is a clear need for an effective measles vaccine for children at six months of age, alternatives to the current EZ vaccine will need to be developed.

Management of Immunization Activities

Many of the obstacles to the reduction of measles morbidity and mortality stem from suboptimal management. Listed below are ten critical areas which determine, in large part, the effectiveness of immunization programs. Each of these areas should be reviewed at least annually at the national and subnational level to assess the appropriateness and effectiveness of policy, strategy, and implementation. Although some factors can be monitored through analyses of routine data (coverage and disease incidence), others require collection of data through supervision, surveys, outbreak investigations, or management audits.

- *Policy.* Is the current immunization policy—for example, schedule—consistent with current technical knowledge (the guidelines of the WHO/EPI Global Advisory Group) and the in-country epidemiology of the EPI diseases? Within-country policy variations may be required to meet different epidemiologic situations (for example, urban slums, rural nomad population).
- *Targets.* Are there national targets for coverage and disease reduction? Are these targets understandable, realistic, and measurable? Do local areas have the responsibility and authority to set local targets, to measure their achievements, and to alter program implementation?
- *Strategies.* Are national and local strategies designed to ensure the achievement of targets? If not, what alterations are needed?
- *Logistics.* Is the national system of vaccine and equipment procurement and distribution adequate to ensure the availability of essential commodities (cold chain, potent vaccines, sterilizers, needles and syringes, vaccination cards) at every immunization delivery point?
- *Training and supervision.* Is there a central authority responsible for ensuring that preservice and inservice education are providing current knowledge on policy, strategy, and practice? Is there a national system of performance assessment, supervision, or surveys which provides data on the quality of immunization delivery (Foster and others 1990; Heiby 1990)?

- *Access.* Do local health jurisdictions have maps of their service areas and a sense of responsibility for the people living within those areas? What percentage of the population has access to immunization services? How can access be increased?
- *Coverage.* What percentage of the at-risk population has been immunized with measles vaccine by twelve months of age? Two methods are used to assess immunization coverage: (a) dividing the number of immunizations reportedly administered under one year of age by the number of surviving infants and (b) completing coverage surveys as recommended by WHO (1988). If local or national targets have not been achieved, what can be done to achieve these targets?
- *Morbidity and mortality reduction.* Is there a routine or sentinel reporting system to monitor trends in measles incidence? Are morbidity reduction targets being achieved? If not, what changes in policy or strategy are needed?
- *High-risk strategy.* Are epidemiologic data available to identify populations at increased risk of dying when infected with measles (high case-fatality rates)? If so, how can strategies be altered to ensure high coverage in those populations?
- *Community participation.* Does the local community participate in immunization through identification of individuals in need of vaccination, publicity of time and place for vaccine delivery, and in disease surveillance?

Surveillance

Achievement of the 1995 morbidity and mortality reduction targets will require improvements in measles surveillance in the following areas:

- Documentation of morbidity and mortality associated with measles infection
- Identification of population groups at high risk of mortality
- The monitoring of trends in measles incidence
- Assessment of the effectiveness of program interventions
- Identification and targeting of program failures in order to reformulate, where necessary, policies and strategies and to define research priorities.

Traditionally, disease surveillance is understood as the routine reporting of morbidity and mortality from health facilities, through intermediary levels, for collation, analysis, and reporting at the national level. This traditional approach to surveillance is flawed on two accounts: (a) measles surveillance data are most useful at the level of collection and (b) achievement of the surveillance objectives listed above requires the use of multiple surveillance methodologies. In table 8-2 we summarize types of surveillance methods useful in effectively managing measles immunization programs.

Table 8-2. Surveillance Methods Used in Measles Control

Surveillance method	*Use of data*
Routine reporting[a]	Monitor trends in incidence over time Identify foci of measles for case investigation
Sentinel surveillance	Monitor trends in incidence over time Monitor demographic and epidemiologic characteristics of cases Identify high-risk populations
Outbreak investigations[b]	Assess community-level morbidity, mortality, and disability Estimate vaccine efficacy Identify populations at high risk Identify risk factors for vaccine failure
Special studies	Assess susceptibility to infection and vaccine seroconversion by serologic surveys Test alternative vaccine strains and delivery schedules Evaluate impact of measles immunization on survival

a. Useful only if reporting is constant over time.
b. Includes cohort, case-control, and cross-sectional studies.
Source: Authors.

Effective surveillance requires timely and effective use of data at each level of the health system: local, district, national. At the local level, every measles case should be considered for its epidemiologic and management relevance. Each case should be assessed as preventable or nonpreventable. Identification of preventability is not a method of faultfinding but a source of information for problem identification and problem solution. Early identification of cases is the necessary first step in effective outbreak control. Case data, together with locally available coverage data, can also be used to assess vaccine efficacy (Orenstein and others 1985). At district and national levels, subunit coverage and incidence data can be used to assess individual area performance and to identify high-risk areas for supervisory attention. Epidemiologic analyses of national data provide important programmatic data for assessing program status, establishing targets, monitoring performance, and providing information for feedback.

Measles Strategies for the 1990s

Countries, regions and WHO are currently in dialogues on the appropriate goal for measles to be achieved over the next decade.

Control, Elimination, Eradication

At the global level, there is considerable debate as to the appropriate long-term measles objective: control, elimination, or eradication. Understanding of the terminology is essential to this dialogue. *Control* means the reduction of measles mor-

bidity and morality to a level that it is no longer a public health problem. *Elimination* implies the interruption of measles transmission in a geographically defined area, island, nation, or continent. *Eradication* is the interruption of person-to-person transmission, the elimination of the virus reservoir, and the termination of prevention procedures. The current WHO/UNICEF goals of 90 percent reduction in morbidity and 95 percent reduction in mortality by 1995 are consistent with measles control.

Measles elimination has been targeted for the United States, Europe, and the Caribbean (PAHO 1990). Although measles elimination has been achieved in certain populations (the Gambia; São Paulo, Brazil; and Cuba), the goal of sustained measles elimination has been more difficult. In the United States, the measles elimination target of October 1, 1982, was not achieved. Although the program was successful in achieving a remarkable 98 percent reduction in measles incidence, persistent transmission has continued primarily in two population groups: urban infants, and older high school and college-age students. In urban areas, the problem has been one of program implementation, the failure to achieve high coverage in infants from poor families. Intensified efforts are being carried out to increase timely immunization of infants in urban communities. Infection in the older age group reflects the accumulation of susceptibles caused by nonimmunization and vaccine failures, many of which relate to immunizations given prior to the currently recommended age of fifteen months. The addition of a second dose of measles vaccine will, in time, eliminate most of the susceptibles among the older age group.

The high cost of achieving and sustaining measles control has prompted some individuals to propose the global eradication of measles (Hopkins and others 1982; Foege 1984). Much of the advocacy for eradication arises out of the successful smallpox eradication program. Hopkins and colleagues have identified similarities and dissimilarities of measles to smallpox: "Both viruses cause infections which are accompanied by typical rashes and which confer life-long immunity; and both viruses have no animal reservoir and do not produce a chronic carrier state in man" (Hopkins and others 1982, p. 1396). Dissimilarities, they report, include "the highly contagious nature of measles" (70 percent attack rate for measles compared with 33 percent for smallpox), the average age of infection (twelve months to eighteen months for measles as opposed to four to five years for smallpox), the age at which a vaccine is effective (six months to nine months for measles as opposed to at birth for smallpox), and the difficulty in diagnosing mild measles as opposed to the ease of diagnosis of both the acute and the recovered case of smallpox (diagnostic pox and scars for smallpox) (Hopkins and others 1982, p. 1396). Other differences include vaccine effectiveness (99 percent for smallpox as against 80 to 90 percent for measles), the stability of vaccine (one year at ambient temperature for smallpox vaccine as opposed to the cold chain required for measles vaccine), and the effectiveness of outbreak control (achievable within one incubation period for smallpox but difficult beyond the first generation for measles). It should also be noted that smallpox eradication required activities in thirty countries for twelve years (the risk of importation was small); conversely, measles eradication, because of the ease of importations, would require work on a global scale.

The mathematical models of measles transmission for industrial and developing countries both predict that if more than 98 percent of young, susceptible children are protected against measles, the disease can be eradicated in large populations. It is important to note, however, that this prediction is based on the assumptions that the population is homogeneous (there are no isolated subpopulations and everyone is equally likely to mix with infected individuals and be vaccinated) and that vaccination failures are rare. These assumptions clearly do not hold in large urban populations. When these assumptions are relaxed, allowing, for example, for variations in susceptibility to infection, in-home exposure, and access to vaccination, the critical level of protection necessary for eradication rises to nearly 100 percent.

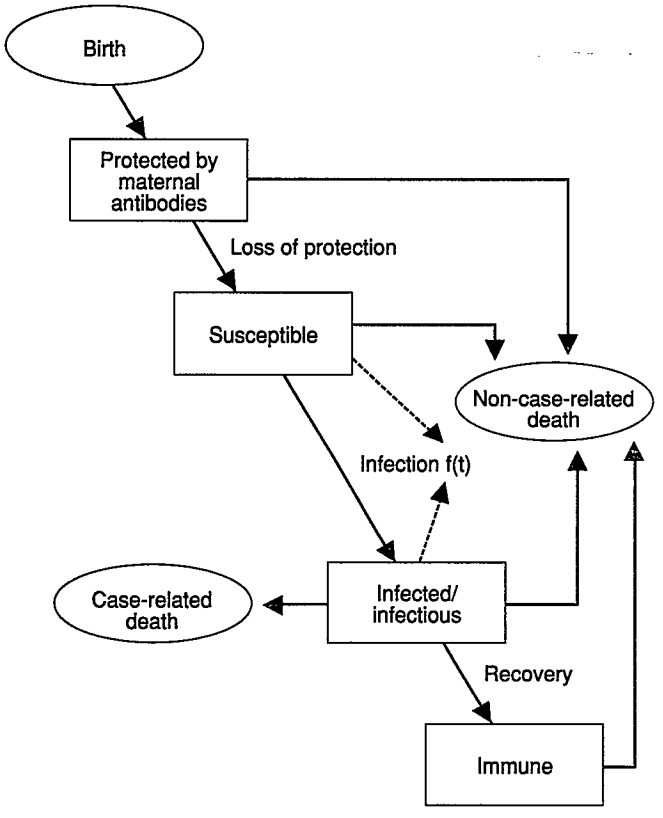
These differences and the data presented in this chapter on disease epidemiology and vaccine efficacy would seem to indicate that measles eradication is not achievable with the current vaccine and the current or projected levels of coverage. This is not to say that measles eradication is not a desirable long-term objective. New, improved vaccines and possibly alternative strategies are needed. However, in a world of limited health resources, careful attention must be given to the opportunity cost of allocating funds to measles eradication instead of to other priority health and development needs.

Mathematical Models

In the past sixty years, many mathematical models of measles transmission and of measles control by vaccination have been developed (for example, Kermack and McKendrick 1927; Dietz 1976; Hethcote 1976; Fine and Clarkson 1982a, 1982b; Schenzle 1989; Anderson and May 1985). These models are based upon the demography and epidemiology of industrial countries and thus describe fairly well the measles patterns in these settings. They do not, however, always accurately describe measles transmission patterns typical of developing countries.

TRANSMISSION. The simplified characteristics of measles transmission at the population level are the same in both industrial and developing countries: infants born to mothers who are immune to measles are protected from infection for several months by transplacental maternal antibodies; the infectivity of measles is high; an individual is both infected and infectious at roughly the same time; case-fatality rates are higher in infancy than in childhood; and recovery from measles results in subsequent long-lasting immunity. Thus, in the simplest model, there are four epidemiologic classes of people: (a) those protected by maternally derived antibodies, (b) those susceptible to infection, (c) those who are infected and infectious, and (d) those who have recovered from measles and are therefore immune. Figure 8-6 traces the progression of individuals among the epidemiologic classes.

Figure 8-6. Stages in the Measles Infection Cycle of an Individual from Birth through Sequence of Epidemiologic Classes to Death



Source: Authors.

Initially, the population consists of infants protected by maternal antibodies and of susceptible individuals who mix randomly. A measles outbreak begins when infected and infectious individuals have contact with a sufficient density of susceptibles. Each time a susceptible individual is encountered, the latter may be infected with a probability proportional to the intensity of exposure. At the earliest stage of the outbreak, most encounters by infectious individuals are with susceptible individuals; therefore, measles spreads quickly. When the illness runs its course in the infected individual, he or she is then immune. As measles transmission progresses through the population, the number of susceptibles decreases whereas the number of immune individuals increases; therefore, it becomes less likely that an infected individual will encounter susceptible individuals and create new infections. If the number of immune individuals is high enough, measles will die out, even though there are still some susceptible individuals in the population: this is the phenomenon of "herd immunity." If, however, susceptibles enter the population (by birth or migration) at a sufficiently high rate, measles may not die out but may instead become endemic.

Immunization programs thus exert their effect at both the individual and the population level: vaccination changes the immune status of the individual and, within the population, it decreases the probability that a susceptible individual will be exposed to measles.

TRANSMISSION MODELS FOR INDUSTRIAL COUNTRIES. In the models of measles transmission and control for industrial countries, the principal epidemiologic assumption is that the rate of measles spread is independent of the spatial density of the host population; the principal demographic assumption is that the host population is not growing. It is generally assumed that vaccination takes place at a precisely targeted age and that all vaccinations are effective. The measles transmission model for industrial countries yields several predictions:

- The number of susceptibles in the population remains the same in the presence and absence of immunization.
- The median age at infection in the population increases after vaccination.
- In the presence of even modest levels of vaccination, the period between epidemic peaks (interepidemic period) will lengthen.
- At any given level of vaccination coverage, the percentage drop in the incidence of measles should be greater than the level of vaccination coverage.
- The proportion of each cohort that must be immunized to interrupt measles transmission is less than 1.0.

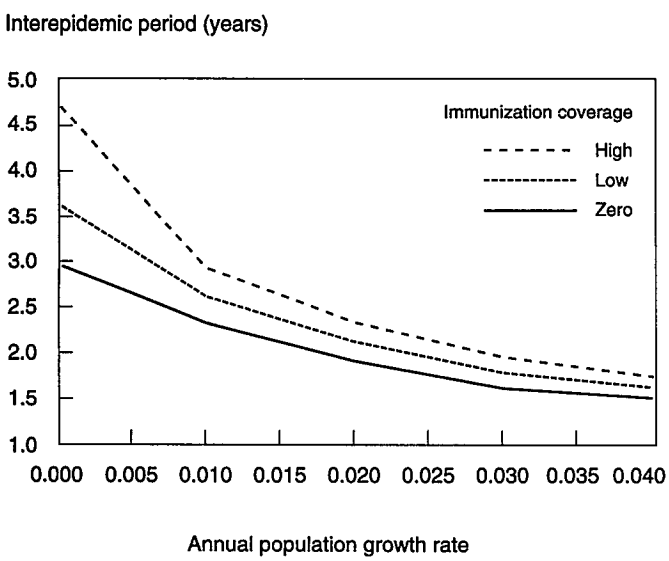
The predictions of this model correspond well to observed pre- and postvaccination measles transmission patterns in the United States and in many European countries.

TRANSMISSION MODELS FOR DEVELOPING COUNTRIES. In contrast, measles transmission models for developing countries explicitly account for the demographic and epidemiologic structure typical of the populations of such countries (John 1990a, 1990b; John and Tuljapurkar 1990; Tuljapurkar and John 1990; Nokes and others 1990), particularly the high rates of population growth. In these models the demographic structure of the host population is determined by the population's fertility and mortality. The distribution of individuals among the four epidemiologic classes at each age is governed by epidemiologic parameters: age pattern of loss of maternal antibodies, age-specific immunization coverage, age-specific infection rate, duration of infectivity, and age-specific case-fatality rate. The demographic structure of the population and the epidemiologic behavior of the infectious disease are linked by the infection rate, which depends on the population's demographic and epidemiologic structure and on the spatial density of the population. More complex developing-country models allow for spatial heterogeneity in infection rates, urban-rural migration, and seasonality in births, deaths, and migration.

The predictions of even the simplest model for developing countries are strikingly different from those of the model for industrial countries:

- The equilibrium proportion of infected individuals in the population (the equilibrium measles prevalence) in-

Figure 8-7. Interepidemic Interval as Function of Population Growth Rate at Different Levels of Immunization Coverage



Note: Interepidemic interval (years) plotted as a function of population growth rate, r, for different levels of immunization coverage (low and high) and for no immunization (i=0.0). In the absence of immunization, the inter-epidemic interval shortens as r increases (3.0 years at r=0.0 to 1.5 years at r=4). At r=0.0, immunization sharply increases the periods between epidemics from 3.0 to 4.6 years, while at r=4.0, immunization increases the inter-epidemic period by only 0.4 years.
Source: Authors.

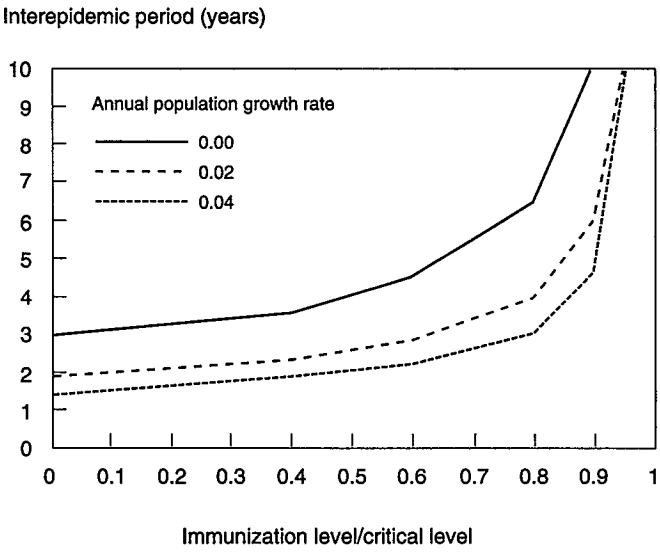
creases as the growth rate of the population increases, both when there is no vaccination in the population and when there is an ongoing vaccination program.

- The mean age at infection in the population need not increase after vaccination, because the remaining post-vaccination cases may be concentrated at the extremes in the youngest and the oldest children; however, the age distribution of cases may change substantially.
- The interepidemic period does not necessarily increase after implementation of a vaccination program in a growing population: when the level of vaccination is a small fraction of the critical level of vaccination required to stop transmission, changes in the interepidemic period are quite small, but when the level of vaccination nears the critical level, the interepidemic period shows a substantial increase (figures 8-7 and 8-8).
- The percentage drop in the incidence of measles, for any given level of vaccination, will be smaller in a growing population than in a nongrowing population: for example, vaccination of 50 percent of the children might induce a drop in measles incidence of 60 percent in an industrial country but of only 52 percent in a rapidly growing population in a developing country.

In contrast to the model for industrial countries, the predictions of the model for developing countries are consistent with the observed effects of immunization programs in Zaire and Cameroon. Between 1980 and 1985 an intensive measles vaccination program in Kinshasa, Zaire, resulted in the vaccination of almost 60 percent of the children who were twelve months through twenty-three months old, yet "two results expected from [measles transmission models]—a reduction in measles incidence greater than the level of vaccination coverage and a shift in the age distribution of measles to older children—have not occurred in this African urban population" (Taylor and others 1988, p. 792). In addition, the predicted increase in the interval between epidemic outbreaks of measles was not observed: epidemics continued to occur biennially. In Yaoundé, Cameroon, the results of a measles vaccination program showed a slight shift upward in the mean age of infection but no corresponding lengthening of the interepidemic interval (Guyer and McBean 1981). In both cases, the observed results are consistent with the prediction of the simplest transmission model for developing countries.

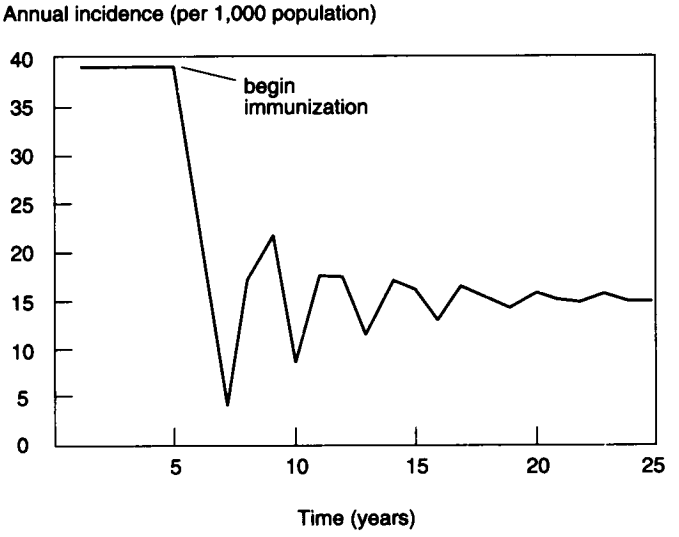
APPLICATION OF MEASLES MODELS: MEASLES INCIDENCE DYNAMICS. When designing vaccination programs for developing countries, one is rarely faced with the task of fine-tuning the details of vaccination delivery, such as deciding whether the optimum age for vaccination is eight months or nine months. Rather, one weighs the merits of substantial program modifications: decreasing missed opportunities,[2] starting vaccination at six months rather than nine months, instituting annual or semi-annual vaccination days, or changing to two-dose schedules. Mathematical models of measles transmission and control are useful tools for vaccination program design and evaluation.

Figure 8-8. Combined Effect of Population Growth Rate and Immunization Coverage on Interepidemic Level



Note: Horizontal axis shows the ratio of achieved level of immunization and the critical level of immunization required to stop measles transmission.
Source: Authors.

Figure 8-9. Simulation Model of Measles Incidence after Immunization



Source: Authors.

Even though one must recognize the importance of parameter assumptions, the models represent powerful tools for evaluating the potential mortality and morbidity effects of different vaccination programs, for anticipating the dynamic behavior of measles in the population, and for examining the influence of demographic variation on measles transmission patterns. For example, for any given specification of the demographic and epidemiologic parameters, the potential effect of a vaccination program can be estimated and alternative vaccination delivery strategies compared; the effects of changes in the host population due to child survival programs, family planning programs, and urbanization can be studied; and the short-run fluctuations in measles incidence can be predicted.

The nature of the short-run fluctuations in measles incidence following an immunization program is crucial in ascertaining whether the WHO goal of a 90 percent reduction of measles incidence can be achieved by 1995. The introduction of any vaccination program reduces the long-run (equilibrium) incidence of measles in the population. The short-run effect on measles incidence is, however, dominated by the fluctuations in annual incidence (figure 8-9). In the simulation model presented here, immunization results in the desired 90 percent reduction in measles incidence within two years (that is, by year seven), but by year nine, the annual incidence is half of the preimmunization level, which would suggest that this immunization program had not achieved the desired goals, despite the evidence from two years earlier. Yet in year ten, there appears to have been an 80 percent reduction from preimmunization levels. In this model, with this set of parameters, the steady estimate of reduction of disease incidence is from 38 to 14 cases per 1,000 population, a reduction of 63 percent. This model, so configured, assumes that fertility, mortality, and immunization parameters remain unchanged during the twenty-five years projected. Thus, ascertaining whether or not an immunization program has achieved its goals, in the short run, is in fact quite difficult; the "success" of the program depends very much on the relative timing of intervention and evaluation.

DISEASE REDUCTION. We have used a simple measles model for developing countries to estimate measles cases and deaths that would occur under the following five different levels of vaccinations in two settings–high-density urban and low-density rural: no vaccination, measles vaccination at nine months, measles vaccination at nine months and decreased missed opportunities, high-titer Edmonston-Zagreb (EZ) or equivalent measles vaccine at six months, high-titer Edmonston-Zagreb or equivalent measles vaccine at six and twelve months. Because an increase in mortality has recently been observed in populations receiving high-titer vaccine (Garenne and others 1991), development of an alternative safe effective vaccine providing 85 percent or higher seroconversion at six months will be needed. To facilitate a comparison among the two populations, a standard population was used with the following characteristics: a birth rate of 48 per 1,000, an infant mortality rate of 100 per 1,000 live births, a population growth rate of 3.5 percent, and a population under ten years of age of 34 percent. The age distribution of cases and age-specific case-fatality rates for each of the two scenarios are listed in table 8-3. For each scenario, estimates were also made of cases occurring prior to vaccination, of vaccine coverage, and of vaccine efficacy, as shown in table 8-4.

Using the measles model for developing countries and the assumptions listed above, we summarize in table 8-5, for both urban and rural settings, the estimates of the number of cases, the number and percentage of cases prevented, and the number and percentage of deaths prevented.

Several important observations can be made from the simulation model: measles mortality is higher in urban areas than in rural areas because of the younger age of infection, an age at which case-fatality rates are higher; at equivalent

Table 8-3. Mathematical Model Assumptions for Unvaccinated Urban and Rural Scenarios: Age-Specific Case-Fatality Rates and Age Distribution of Cases
(Age distribution in 1990)

		Age distribution	
Age (months)	*Case-fatality rate*	*Urban*	*Rural*
<6	—	0	0
6–8	4	18	3
9–11	4	19	6
12–23	5	40	14
24–35	3	10	16
36–47	2	8	18
48–59	1	5	20
60–119	.05	0	23

Source: Authors.

Table 8-4. Mathematical Model Assumptions for Measles: Subjects Immune from Infection at Time of Vaccination, Coverage, and Efficacy of Vaccine

	Urban			Rural		
Scenario	Immune	Coverage	Efficacy	Immune	Coverage	Efficacy
Measles vaccine at 9 months	30	60	85	10	60	85
Eliminate missed opportunities	30	80	85	10	80	85
EZ[a] at 6 months	10	80	85	2	80	85
EZ[a] at 6 months and 12 months	10	80 60	85 95	2	80 60	85 95

a. Edmonston-Zagreb or equivalent measles vaccine providing 85 percent seroconversion and protection when given at six months of age.
Source: Authors.

levels of coverage, rural strategies are more effective in reducing morbidity and mortality; use of an effective vaccine at six months significantly increases the effectiveness of urban immunization; and two-dose schedules further increase program effectiveness. For simplicity, these calculations do not take into account herd immunity; they do, however, provide an estimate of the long-term effect of alternative strategies for the delivery of measles vaccine. Maximum reductions in morbidity and mortality are obtained with the two-dose vaccine schedule in which a vaccine is used that is effective when administered at six months of age. Coverage levels used in these models represent those currently being achieved by well-managed immunization programs in developing countries. Few countries have been able to achieve and maintain the 95 percent levels achieved in industrial countries.

Simulations are only as accurate as the assumptions and the model used. The assumptions used above reflect data collected from the city of Lagos, Nigeria, Kinshasa, Zaire, and the rural areas of Matlab, Bangladesh. It is our expectation that these data will contribute to the dialogue on alternative measles strategies. The model, reflecting the currently achieved levels of coverage and vaccine efficacy, projected reductions in morbidity and mortality significantly below the 90 percent morbidity and 95 percent mortality reduction targets established by WHO and affirmed at the 1990 World Summit for Children. According to the model, a two-dose schedule with a vaccine effective at six months of age has the greatest potential for moving operational programs toward the global targets. Further improvements in vaccine coverage and effectiveness will be required to ensure the elimination of measles as a significant cause of childhood morbidity and mortality.

COST-EFFECTIVENESS OF ALTERNATIVE STRATEGIES. Given the above results, we can now consider the costs of the alternative strategies. Costs are predicated on an average cost of $15 per fully immunized child with 40 percent of the cost, or $6, allocated to measles. The cost profile (the contribution of each cost component to total cost) is based on the delivery modality for immunizations in fixed sites (Brenzel 1990). For each alternative strategy, assumptions were made which would change original cost estimates, that is, the incremental costs attributable to each strategy. These assumptions are enumerated below. Costs are assumed to be the same in both urban and rural settings with the exceptions noted.

- Measles immunization at nine months.
- Measles immunization at nine months but a 50 percent increase in vaccine use so that vaccines represent 10 percent of total costs and a 10 percent increase in supervision costs.
- Edmonston-Zagreb or equivalent vaccine given at six months are $6 (the same as measles immunization at nine months). Cost of vaccine is same as currently used measles vaccine. Delivery pattern and sites remain the same. Although one might expect declining average costs because of increasing volume, the effect is probably quite small and thus negligible to average cost.
- Edmonston-Zagreb or equivalent vaccine given at six months and twelve months: cost for second dose is the same

Table 8-5. Simulation Estimates of Measles Cases and Deaths in High-Density Urban and Low-Density Rural Scenarios: Developing Country Model

	Urban						Rural					
Scenario	Cases	Cases prevented	Cases prevented (percent)	Deaths	Deaths prevented	Deaths prevented (percent)	Cases	Cases prevented	Cases prevented (percent)	Deaths	Deaths prevented	Deaths prevented (percent)
No vaccination	36,400	n.a.	n.a.	1,452	n.a.	n.a.	36,400	n.a.	n.a.	806	n.a.	n.a.
Measles vaccine at 9 months	25,744	10,656	29	1,025	425	29	20,193	16,207	45	456	350	45
Vaccine at 9 months and eliminates missed opportunities	22,192	14,208	39	885	567	39	14,791	21,609	59	339	467	58
EZ[a] at 6 months	14,123	22,277	61	563	889	61	12,165	24,235	67	269	537	67
EZ[a] at 6 and 12 months	9,051	27,349	75	361	1,091	75	5,844	30,556	84	140	660	83

n.a. Not applicable.
a. Edmonston-Zagreb or other vaccine that achieves 85 percent seroconversion and protection when administered at six months of age.
Source: Authors' calculations.

Table 8-6. Efficacy and Cost of Alternative Strategies to Increase Measles Coverage in Urban Areas

Strategy	Cases prevented	Deaths prevented	Unit cost $	Coverage (percent)	Doses administered	Total annual cost	Total incremental cost	Total cost per case prevented	Total cost per death prevented	Incremental cost per case prevented	Incremental cost per death prevented	Total cost per DALY	Incremental cost per DALY
Measles vaccine at 9 months (baseline)	10,656	425	6.00	60	30,600	183,600	n.a.	17.23	432.00	n.a.	n.a.	14.90	n.a.
Vaccine at 9 months and missed opportunities	14,208	567	6.42	80	40,800	261,936	78,336	18.44	461.97	22.05	551.66	15.93	19.02
EZ[a] at 6 months	22,277	889	6.00	80	40,800	244,800	61,200	10.99	275.37	5.27	131.90	9.50	4.55
EZ[a] at 6 months and 12 months	27,349	1,091	6.00 6.00	80 60	40,800 27,000	406,800	223,200	14.87	372.87	13.37	335.14	12.86	11.56

n.a. Not applicable; increment is determined in relation to this baseline.
a. Edmonston-Zagreb or equivalent vaccine providing 80 percent seroconversion when given at six months of age.
Source: Authors' calculations.

as first dose at six months. Assume that second dose is administered at routine vaccination session or child health visit and therefore does not require additional personnel or outreach. A decrease in volume may predictably increase the average cost of the second dose only if the average cost curve is quite steep.

Using the measles model for developing countries presented earlier, the annual number of cases and deaths in children under ten that would be prevented by each alternative strategy in each scenario was tabulated for use in the cost-effectiveness calculations (tables 8-6 and 8-7). In these calculations, cases and deaths prevented represent the annual number of cases and deaths prevented for the entire cohort of children under ten in any given year. Total annual costs, however, only reflect costs incurred in a single year to immunize the currently eligible children (those under twelve months of age). Costs are expressed in 1990 dollars. In order to compare these results with previous studies, the costs must be converted to the relevant year for which the study data were reported.

The cost per disability-adjusted life-year was calculated under the assumption that a death averted "buys" about sixty years of life or, if one discounts future life-years gained at 3 percent, the annuity stream reveals that a prevented death of a child from measles buys about 29 disability-adjusted life-years. The calculation does not account for DALYs lost to disability caused by measles, because it is estimated that more than 95 percent of years of life lost from measles are due to premature mortality and not to disability (Duflo and others 1986). More refined estimates of DALYs would need to take into account disability caused by measles complications and the concomitant cost in healthy life-years lost. Results of the cost-effectiveness studies are summarized in tables 8-6 and 8-7.

The tables give relative estimates of the cost-effectiveness of alternative strategies to increase measles coverage, notwithstanding all the caveats and assumptions built into the analysis. For urban populations, the most cost-effective strategy appears to be administering Edmonston-Zagreb or equivalent vaccine to children at six months of age. This strategy is also the most cost-effective for rural populations, although use of the current

Table 8-7. Efficacy and Cost of Alternative Strategies to Increase Measles Coverage in Rural Areas

Strategy	Cases prevented	Deaths prevented	Unit cost $	Coverage (percent)	Doses administered	Total annual cost	Total incremental cost	Total cost per case prevented	Total cost per death prevented	Incremental cost per case prevented	Incremental cost per death prevented	Total cost per DALY	Incremental cost per DALY
Measles vaccine at 9 months (baseline)	16,207	350	6.00	60	30,600	183,600	n.a.	77.33	524.57	n.a.	n.a.	18.09	n.a.
Vaccine at 9 months and missed opportunities	21,609	467	6.42	80	40,800	261,936	78,336	12.12	560.89	14.50	669.54	19.34	23.09
EZa at 6 months	24,235	537	6.00	80	40,800	244,800	61,200	10.10	455.87	7.62	327.27	15.72	11.29
EZ[a] at 6 months and 12 months	30,556	666	6.00 6.00	80 60	40,800 27,000	406,800	223,200	13.31	10.81	15.56	706.33	21.06	24.36

n.a. Not applicable; increment is determined in relation to this baseline.
a. Edmonston-Zagreb or equivalent vaccine providing 80 percent seroconversion when given at six months of age.
Source: Authors' calculations.

measles vaccine at nine months and use of every missed opportunity along with the current measles vaccine appear to be almost as effective. At least for rural populations, there is no significant difference in the cost-effectiveness of the first three strategies, given the limits of the analysis.

Achieving the 1995 Measles Targets

In 1989, WHO established global EPI targets for the decade of the 1990s: that coverage levels will surpass 80 percent in all countries or areas by the end of 1990 and that levels of 90 percent, in the context of comprehensive maternal and child health services, can be achieved by the year 2000. At the September 1990 World Summit for Children, the WHO 1995 targets for morbidity and mortality reduction were affirmed, 90 percent and 95 percent, respectively. Although global levels of immunization coverage have increased dramatically during the last decade, representing a major achievement of national governments and their collaborating partners, there is still a significant gap between the current levels of coverage and disease reduction and the 1990 targets, as shown in table 8-8.

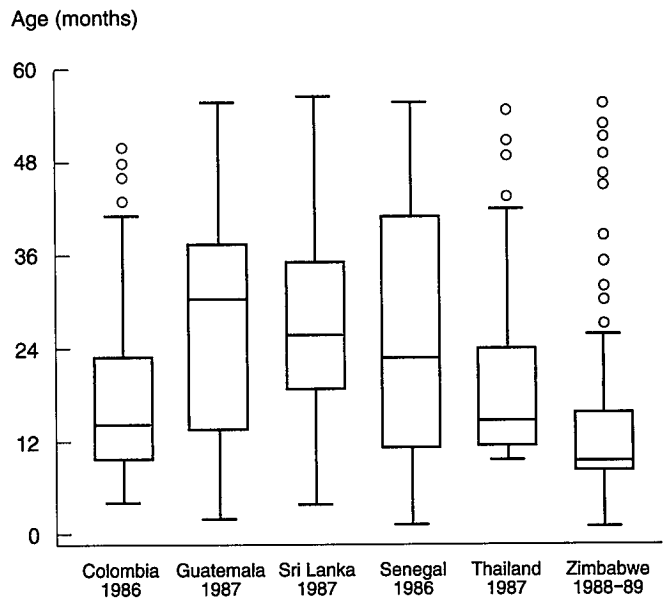
Achievement of the 1995 and 2000 targets will require increases in both coverage and vaccine efficacy. Eleven strategies, some already a part of the EPI program, hold the potential to increase levels of coverage, increase vaccine efficacy, decrease measles incidence, and decrease measles mortality: (a) vaccination in the first year of life, (b) reduction of missed opportunities, (c) increase in community partnership, (d) registration and follow-up of newborns, (e) use of accelerated immunization strategies, (f) vaccination of high-risk groups, (g) adoption of two-dose measles vaccine schedules, (h) provision of vitamin A supplementation in vitamin A–deficient areas, (i) treatment of severe cases of measles with vitamin A, (j) effective treatment of measles complications, and (k) expansion of the infrastructure. The first six of these strategies, in part developed from experience in the developing world, are important components of the current United States initiative to achieve measles control (United States, National Vaccine Advisory Committee 1991).

Table 8-8. Measles Coverage and Estimated Disease Rediction, by WHO Region, 1989
(percent)

Region	*Measles coverage*	*Estimated reduction in morbidity*[a]
Africa	47	40
Americas	73	62
Mediterranean	70	60
Europe	85	72
Southeast Asia	58	49
Western Pacific	90	77

Note: 1995 target is 90 percent for both measles coverage and morbidity reduction.
a. Coverage times vaccine efficacy (85 percent).
Source: WHO internal data.

Figure 8-10. Age of Measles Vaccination of 48–59-Month-Old Children in Six Countries



Note: For each population, the median age at immunization is indicated by line inside box. The median age of immunizations administered at ages greater than the median age (approximately the 75th percentile) are graphed as the upper bar of the box. The line extended from the top of the box ends at upper boundary: the observation closest to but less than the sum of the 75th percentile plus 1.5 times the difference between the 25th and 75th percentile. Any observations greater than the boundary were deemed outliers and are plotted individually. The lower boundary was constructed in an analogous manner.
Source: Authors.

VACCINATION IN THE FIRST YEAR OF LIFE. Measles vaccine is effective when administered to a susceptible individual prior to or at the time of exposure to measles. The World Health Organization and UNICEF have emphasized the importance of vaccination in the first year of life in developing countries. Vaccination of older children is less effective in developing countries, because many children (the number increasing with age) may have already become immune through infection with wild virus. Using data from demographic and health surveys (Boerma and others 1990), we provide in figure 8-10 a boxplot of the age distributions of card-documented immunizations from six countries. Except for Zimbabwe, the boxplots show a pattern of delayed measles vaccination.

Increased attention to vaccination in the first year of life, at nine months for the Schwarz strain and six months for alternative vaccines that provide high rates of seroconversion and protection, will increase the probability that a dose of vaccine will be administered to a susceptible infant and thus, depending on age-specific rates of vaccine efficacy, increase program effectiveness in achieving disease reduction.

REDUCTION OF MISSED OPPORTUNITIES. The term "missed opportunities" is defined as contacts of a target-age individual (infant, child, or reproductive-age woman) in need of one or more vaccines with a health facility capable of providing that vaccine and a failure of that contact to provide the needed

vaccine(s). There are two types of missed opportunities for immunization: missed vaccination opportunities and missed health facility opportunities.

Missed vaccination opportunities occur when an individual attending a vaccination session fails to receive a needed vaccine or receives one inappropriately timed by age or intervaccination interval. A review of fifteen published articles has documented missed vaccination rates ranging from 8 percent in Mozambique to 76 percent in Indonesia; the median for the fifteen countries was 49 percent (Hirschorn 1990; Grabowsky 1991).

Missed opportunities are also being identified in industrial countries. Investigation of an urban outbreak of measles in the United States identified missed opportunities for measles immunization in fifteen of twenty-six measles cases in an urban outbreak among preschool children (Hutchins and others 1989). Missed opportunities were also documented as a significant factor in the 1990 measles epidemic in the United States (United States, National Vaccine Advisory Committee 1991).

Four methods have been used to assess the rate of missed opportunities:

- *Record reviews.* Facility-held records, vaccination registers, or individual patient immunization cards are reviewed to assess whether all indicated antigens were administered on recorded dates of vaccination contact.
- *Exit interviews.* Child caretakers and reproductive-age women leaving a clinic during a time at which immunizations are being administered are interviewed by health staff. Immunization records are examined for missed or inappropriately timed immunizations (early for age or too short an interval between doses).
- *Clinic observation.* Supervisory staff observe immunization sessions to identify errors in screening, referral, or immunization.
- *Coverage surveys.* As part of surveys to assess immunization coverage, data from individual client-held record cards are reviewed for missed opportunities for immunization on days of recorded attendance at an immunization session and for inappropriately timed immunizations (Cutts, Glik, Gordon, and others 1990). Analyses of these data are facilitated by use of COSAS, a software package which analyzes coverage survey data for coverage, age, intervals between immunizations, and missed opportunities (Boyd 1991).

Ten major causes for missed opportunities for immunization have been identified (Hirschorn 1990).

- Coexistent illness as determined by health worker or child caretaker. In contrast, note that WHO policy calls for immunization at every opportunity. "It is particularly important to immunize children suffering from malnutrition. Low-grade fever, mild respiratory infections or diarrhea, and other mild illnesses should not be considered contraindications to immunization. The decision to withhold immunization should be taken only after serious consideration of the individual child and community. Immunization of children too ill to require hospitalization should be deferred for decision of hospital authorities" (WHO/EPI 1984, p. 15).

Although recent data suggest decreased rates of seroconversion in children with respiratory infection (Krober 1991), an overall assessment of risks and benefits mandates vaccination of both sick and well children. Because of the risk of nosocomial spread of measles, all children from six months through five years of age who are admitted to a hospital should receive measles vaccine on admission if there is no documentation of age-appropriate measles immunization.

- Incorrect screening by the health worker. (Screening errors relate to a lack of understanding of national vaccination schedule, difficulties in calculating the interval between recorded date of birth and current date, failure to check all antigens, clerical error because of fatigue, or lack of motivation.)
- Vaccine not available.
- Clinic too crowded or disorganized to handle the demand.
- Absence of staff, vaccine, or transport resulting in the cancellation of a scheduled immunization session.
- Mothers too busy to wait, not informed that they should wait, or dissatisfied.
- Health workers' fear of wasting measles vaccine, resulting in refusal to open a multidose vial for one child (WHO and UNICEF recommend opening a vial of vaccine even for one child).
- Acceptance by health worker of an oral history of measles or measles vaccination as a reason for nonimmunization. (Serologic studies have documented the unreliability of histories of measles and measles immunization; all eligible children without written proof of measles vaccination should be immunized with measles vaccine.) The failure of child caretakers to bring the immunization cards to clinic also contributes to this problem.
- Unwillingness of health workers to administer more than one antigen at a time. (Studies have documented the safety and efficacy of simultaneous separate multiple antigen vaccine administration [Foege and Foster 1974]).
- Nonimmunization of individual identified for immunization. This occurs when immunization cards are returned to parents prior to the completion of all immunizations. Such situations may arise when children have been referred for multiple immunizations, for example, DPT, OPV, and measles. Delaying the return of the vaccination card until all antigens required for that vaccination session are administered can eliminate this problem.

When persons eligible for immunizations visit health facilities that are capable of delivering vaccine and vaccines are not given, a missed health facility contact has occurred. Such missed contacts happen in clinics in which administration of vaccines is limited to certain days (infant welfare)

or groups (well children). And all too commonly they occur because curative-oriented health workers fail to assess immunization status. Although these missed opportunities may be the most common ones, they are less well documented. Identification of such missed opportunities is facilitated by a unified clinic- or patient-held record system in which immunization and all health contacts are entered on the same record. In the Central African Republic, a comparison of dates of all health facility contacts with opportunities for measles immunization showed that use of all opportunities would have achieved a measles vaccine coverage of 76 percent, rather than the actual 54 percent (Roungou 1991). In Guinea, a community survey estimated that 30 percent of the opportunities for measles immunization had been missed (Cutts, Glik, Gordon and others 1990).

Integrated service delivery in which all health facility contacts are used to screen and immunize all eligible persons can reduce this problem. Although the transition from specialized immunization clinics to routine immunization is initially difficult, the shift to a "comprehensive" approach to vaccine delivery has been effective in reducing the missed health facility opportunity. Pioneered by Shanti Ghosh in Delhi, India, the practice of screening and immunizing all emergency department and outpatient cases prior to their contact with a physician or nurse has been effective in reducing missed opportunities, increasing coverage, and reducing disease morbidity in Zimbabwe and Mozambique (Ekunwe 1984; WHO/EPI Zimbabwe 1989; Hirschorn 1990). Yach and others (1991) estimated 240,000 missed opportunities for measles vaccination per year at two tertiary-level referral hospitals in South Africa. In an investigation of an inner-city measles outbreak in the United States, 38 percent of cases had received DPT or diphtheria-tetanus vaccine at an age when they were eligible to receive measles vaccine (Hutchins and others 1989). In the United States, extension of immunization to contacts with public assistance could significantly increase coverage (United States, National Vaccine Advisory Committee 1991).

INCREASE IN COMMUNITY PARTNERSHIP. Community partnership in immunization is important to the achievement and maintenance of high levels of vaccine coverage. This is well demonstrated in Indonesia, where the PKK, a national organization of women, has become a major partner in childhood immunization. Vaccination coverage provided by outreach vaccinators that had been in the range of 15 to 30 percent increased to 70 to 90 percent in villages where the PKK was active. The PKK organizes the clinics and participates in clinic activities, including the preparation of advance publicity, the weighing of children, the recording of weights, nutrition education, and the distribution of contraceptives. In Liberia and Mozambique, the participation of local chiefs, traditional birth attendants, and village health committees has been effective in increasing coverage (Cutts and others 1988; Bender and Macauley 1990).

Polio eradication is providing many new strategies to increase partnerships. This is best exemplified by the Rotarians around the world, both in the provision of funds (over $200 million) and in the active involvement of local Rotarians in social mobilization and direct assistance in vaccine delivery activities. Prime emphasis is being given to the training of community volunteers to identify and refer eligible children for immunization. In areas where such programs are operational (for example, Ijeru-Ekiti, Nigeria), coverage rates are over 90 percent and drop-out rates are near zero.

REGISTRATION AND FOLLOW-UP OF NEWBORNS. In rural areas where population movement is limited, the enumeration of births and the monitoring of immunization status through the first year of life has proved effective in increasing coverage. In Oman, health facility records of immunization are maintained by month of birth (health facility usage is over 95 percent); a monthly review of immunization records of one-year-old children provides a mechanism for assessing coverage and identifying defaulters for follow-up. Coverage in this population is over 98 percent (Foster 1989). In other places, maintenance of village registers serves the same purpose. Door-to-door visits have also been used to register the at-risk population, identify susceptibles, and refer eligibles for vaccination.

USE OF ACCELERATED IMMUNIZATION STRATEGIES. During the last decade, WHO and UNICEF have promoted accelerated immunization activities as a mechanism to increase coverage (WHO/UNICEF 1985). Historically, immunization days date back to the 1950s, when Sunday vaccination days were instituted to increase polio coverage in the United States. Biennial OPV polio campaigns have been used widely in Latin America, especially in Brazil, and have been credited with the near elimination of that disease from the Western hemisphere (de Quadros, Andrus, and Olive 1991).

Largely through the personal advocacy of the executive director of UNICEF, national immunization days have been established to increase vaccination coverage. Countries using this strategy have included Colombia, Turkey, Senegal, Nigeria, and Côte d'Ivoire. These accelerated strategies have been promoted to achieve several important objectives:

- To elevate the health sector in general, and immunization programs in particular, to the national political agenda. Political leaders have provided leadership in the planning, promotion, and implementation of immunization days.
- To change the public perception of immunization from that of an intermittently available service to that of a basic human right.
- To increase business, voluntary organization, and public support for immunization programs.
- To increase access to immunization services.
- To increase immunization coverage and reduce morbidity and mortality.

Immunization days in many countries, for example, Colombia, Turkey, and Côte d'Ivoire, have been spectacularly successful in achieving their political and coverage targets. Immuniza-

tion coverage rates have increased to levels in excess of 90 percent; rates of disease incidence have been dramatically reduced.

From the perspective of maintaining high levels of coverage, however, the value of these accelerated strategies has been questioned on four accounts:

- Opportunity cost—the diversion of limited health resources from essential preventive and curative health services to immunization activities.
- Quality and safety—the inability to provide the quantity and quality of supervision required to ensure compliance with basic technical guidelines (Bryce, Cutts, and Saba 1990).
- Cost-effectiveness—the high cost required for a major campaign (vaccine, supplies, cold-chain equipment, personnel, transport, and publicity) and the relative inefficiency of campaigns in providing vaccines to those at greatest risk, children in the first year of life.
- Sustainability—the value of campaigns in promoting and maintaining high rates of vaccine coverage and disease reduction over time.

The expanding experience with accelerated strategies is prompting a shift of policy dialogue from the question of their appropriateness to the question of where, when, and under what conditions accelerated strategies are useful. The poliomyelitis experience in the Americas, especially Brazil, has shown that immunization days are effective in increasing coverage and decreasing disease incidence and can be sustained over time (de Quadros, Andrus, and Olive 1991). For measles, experience in India demonstrated that annual single-day measles campaigns in a village without access to routine vaccine services was effective in achieving and maintaining measles control (John, Ray, and Steinhoff 1984). In Liberia, a country in which only 40 percent of the population had access to health facilities, annual immunization weeks for five consecutive years, epidemiologically timed to precede the measles season, have succeeded in increasing immunization coverage from 15 to 60 percent (CCCD 1990). During 1989, approximately 40 percent of annual immunizations were administered during this vaccination week. Of special importance to the success of these campaigns was the local partnership in the planning, funding of local costs, and implementation of the vaccination weeks. This system, a viable model for many parts of Africa, has unfortunately been destroyed by civil war.

Five conditions are suggested as criteria for the appropriate use of accelerated strategies in achieving local and national EPI targets:

- *Low access* (50 percent access of target population to a facility regularly providing vaccines). In areas of low access to health facilities and where the potential for outreach is limited, accelerated strategies provide an attractive option in achieving coverage and disease reduction targets.
- *Frequency and repeatability.* As needed, accelerated strategies should be conducted annually, as in the Indian example above, or twice a year, as in the polio campaigns in Latin America. For measles, timing the activity to the preepidemic season maximizes effect and cost-effectiveness.
- *Decentralization.* As sustainability and effectiveness are very dependent on local participation, responsibility for planning, vaccine delivery, supervision, and evaluation should be decentralized to the level of implementation, for example, district, sector, and so on.
- *Targeting.* Target age groups for immunization, selection of antigens, and timing of accelerated activities need to be based on relevant local data about the availability of the population, physical access to that population, and disease epidemiology.
- *Safety.* Because immunizations (perhaps the most cost-effective of all health interventions) are not totally safe—for example, in the transmission of pathogens through use of nonsterile procedures—systems to ensure quality must be developed and sustained. Systems of training and supervision need to ensure the quality of vaccine delivery as part of accelerated strategies. This includes maintenance of the cold chain and sterilization, appropriate age and intervals for immunization, and instructions to the mother about the need for return visits to complete immunization.

VACCINATION OF HIGH-RISK GROUPS. Four groups of children are particularly at risk from measles and should be vaccinated or, in certain cases, revaccinated. Among refugees, measles has been identified as the main cause of mortality in new refugee populations (Toole and Waldman 1988). Ethiopian refugees in Sudan show a measles CFR of 33 percent (Shears and others 1987). Measles immunization has been identified as a "high priority in emergency relief programs, second only in importance to the provision of adequate food rations" (Toole and others 1989, p. 381).

Hospitalized children, especially those who are severely malnourished, are, if infected, at high risk of measles-associated mortality. Mortality in malnourished children infected with measles in a hospital setting is frequently above 50 percent. Among sixty nosocomial infections requiring admission to a South African hospital, measles and its complications accounted for twenty-eight (47 percent) of readmissions and seven deaths (Cotton and others 1989). All pediatric admissions without written documentation of measles immunization at an appropriate age should be given measles vaccine on admission. Children vaccinated prior to twelve months of age should be reimmunized.

Nosocomial transmission of measles is common in the developing world. In a study in Côte d'Ivoire, 69 percent of measles patients seen at an urban health facility had attended a health facility eight to twenty-one days prior to onset of measles (Foulon and others 1983; Klein-Zabban and others 1987). Nosocomial transmission has also been reported from Taiwan (Gao and Malison 1988); severity of illness was greater

in children who had attended the clinic for illness than in those who had attended for well baby care ($P < .01$). Immunization at every opportunity, as advocated by WHO, would have prevented most of these cases.

In urban populations in western and central Africa, measles is primarily a disease of the first two years of life, an age at which CFRs are highest (Taylor and others 1988). Children in urban slums have been identified as at increased risk for high measles mortality (low coverage and low age of infection), and thus such slums are a priority area for targeted immunization (Coetzee, Berry, and Jacobs 1991). Lot quality assessment sampling has been used to identify low coverage areas in Kinshasa, Zaire. Priority attention to these high-risk groups will have maximum effect on measles-associated mortality. Three guides to improve urban immunization have recently been published (UNICEF 1989; Claquin 1991; Cutts 1991). Targeting vaccine to places and groups for which epidemiologic data document increased mortality risk (for example, supplementary feeding centers and girls in poor homes in Bangladesh [Bhuiya and others 1987]), will increase the efficiency of immunization in achieving the mortality reduction goal.

ADOPTION OF TWO-DOSE MEASLES VACCINE SCHEDULES. Ninety percent coverage with a vaccine producing 90 percent efficacy will provide protection to 81 percent of vaccinees, significantly less than the 1995 disease reduction target of 90 percent. Two-dose schedules have the potential to facilitate the achievement of the 90 percent measles reduction target by reducing the number of primary vaccine failures. Two-dose schedules can use the currently available Schwarz vaccine or an improved vaccine providing 85 percent seroconversion for those vaccinated at six months of age. Three two-dose schedules are provided as examples:

- In dense urban areas where risk of infection is highest in the first two years of life, two doses of EZ or equivalent vaccine need to be given as early as possible, for example, at six months and twelve months of age.
- In rural areas with low coverage, immunization at nine and fifteen months of age with Schwarz or equivalent vaccines would be appropriate.
- In countries where high immunization coverage has shifted the age distribution of measles cases to schoolchildren, a second dose of measles vaccine at school entry should be considered. School immunization not only decreases infection in susceptible older children but also decreases the risk of morbidity and mortality in their preschool siblings (measles transmission in schoolchildren has been identified as a source of infection for their high-risk preschool siblings). In Burundi, twenty-five out of twenty-eight cases of measles in school-age children were index cases in their households and the source of infection for thirty-one secondary cases, twenty-eight of whom were younger siblings (Chen 1990). Introduction of two-dose schedules has reduced measles transmission to very low levels in Murmansk and Pskov areas in the former U.S.S.R. and in Czechoslovakia (Davis 1991).

VITAMIN A SUPPLEMENTATION IN DEFICIENT AREAS. The World Health Organization has recommended that vitamin A supplementation become a routine part of immunization programs. Specifically, it recommends the administration of 200,000 international units (IU) to mothers at time of delivery or during the next four weeks, and 25,000 IU at each immunization contact beginning at six weeks of age and with at least four-week intervals (WHO/EPI 1989a, 1992). This recommendation is based on data from Indonesia and India showing that vitamin A supplementation to children in an area of vitamin A deficiency reduced overall mortality (Rahmathullah and others 1990; Sommer 1990). Although Rahmathullah and colleagues (and other researchers) did not show a clear reduction in measles or other specific cause of mortality, there is a growing consensus that vitamin A supplementation in deficient areas will reduce measles case-fatality rates and increase child survival.

TREATMENT OF SEVERE MEASLES WITH VITAMIN A. Therapeutic doses of vitamin A are now recommended for children with severe cases of measles. In a placebo-control double-blind study in South Africa, the risk of death or severe measles complication was reduced by half (RR 0.52 95 percent CI 0.35–0.74) through administration of 400,000 IU of retinyl palmitate (Hussey and Klein 1990).

EFFECTIVE TREATMENT OF MEASLES COMPLICATIONS. Most measles deaths are due to complications, a high proportion of which can be effectively treated through standard treatment practices. Data from Senegal suggest that treatment in the first few days of illness can reduce measles CFRs by 78 percent (Garenne 1992).

EXPANSION OF THE INFRASTRUCTURE. In many areas, at-risk infants have limited access to vaccination services. Development of new vaccine delivery points in such places has to be a long-term priority.

Research Priorities

Improved vaccines and implementation strategy will be required to achieve the 1995 targets. Research is a continuing priority.

OPERATIONAL RESEARCH. The currently available tools (measles vaccines, cold chain, disposable and reusable needles and syringes) have the potential of significantly aiding the effort to reduce measles and measles-associated morbidity and mortality. Operational research is needed to identify the optimal use of these tools to achieve the maximum effect, for example, use of two-dose schedules, targeting of high-risk groups, and accelerated vaccination strategies in urban areas.

VACCINE DEVELOPMENT. Although the current more heat stable vaccine is a highly effective vaccine, further improvements in measles vaccine could significantly increase the effectiveness of efforts to control measles. The ideal criteria for a measles vaccine in the developing world, based on experience acquired in the 1980s and the expected improvements to be gained by the introduction of vaccine capable of providing protection at six months of age, have not yet been met. Listed below are suggested criteria for such a vaccine:

- *Heat stable at 37°C for twelve months.* In the developing world, the areas with highest measles-associated mortality, lack of a reliable cold chain limits many health workers, especially private practitioners, from providing immunization. Resources for fuel and refrigerator maintenance, repair, and replacement are expected to shrink during the next decade.
- *Ability to achieve 95 percent seroconversion and life-long protection when administered at three months of age or earlier.* Access to health facilities is inversely related to age—the younger the age at immunization, the greater the probable contact of that child with health facilities and the opportunity for immunization. An effective vaccine for three-month-old infants would prevent almost all the measles cases that occur before nine months of age. As increasing numbers of infants in the developing world are born to mothers whose antibodies resulted from immunization rather than wild virus infection, infection in the first six months of life may increase in frequency. Immunization in the first few months of life will be needed to address this problem. A major initiative to develop such a vaccine is under way (Bart and Lin 1990).
- *Prepackaged in a single-dose non-reusable syringe.* Single-unit packaging would facilitate expanding vaccine delivery to private practitioners and nurse-midwives operating outside of the health facilities. Use of self-destruct syringes would eliminate sterilization costs and the risks of human immunodeficient virus (HIV) and hepatitis B transmission through reuse of syringes.
- *Affordable.* Vaccine cost should be in the range of the current $0.10 to $0.15 per dose.

Conclusions

Measles immunization is a proven, cost-effective primary health care intervention capable of reducing morbidity and mortality and increasing child survival. The use of current vaccines and strategies will not, however, achieve the targets (90 percent coverage, 90 percent morbidity reduction, and 95 percent mortality reduction) endorsed at the 1990 World Summit for Children. Five priorities have been identified for the 1990s:

- Development of a heat-stable vaccine providing 85 percent or higher protection when administered at six months of age or earlier.
- Operational research to ensure maximum effective use of available technologies within the epidemiologic and resource realities of the local environment.
- Strengthened decentralized management and ownership in the planning, implementation, and evaluation of immunization program.
- Development and use of management and disease information systems to strengthen decisionmaking, implementation, and evaluation.
- Continued awareness and commitment of bilateral and international technical assistance agencies on the need of developing countries for continuing foreign-exchange support for vaccines and cold-chain equipment.

Notes

We appreciate and acknowledge Felicity Cutts, Michael Deming, Michelle Garenne, Mark Grabowsky, Rafe Henderson, Bert Hirschorn, Laurie Markowitz, Walter Orenstein, and Akanne Sorungbe for their thoughtful review of sections of this chapter in manuscript form. The expert clerical support of Pat Jennings, Judith Clark, Quin Long, and Arvis McCormick is also recognized.

1. Except where noted otherwise, all dollar amounts are current U.S. dollars.
2. Missed opportunities: contacts between a child needing vaccination and a health facility with vaccine delivery capability at which needed vaccinations are not provided.

References

Aaby, Peter. 1988. *Malnourished or Overinfected: An Analysis of the Determinants of Acute Measles Mortality*. Copenhagen: Laegeforeningens Forlag.

Aaby, Peter, Jette Bukh, I. M. Lisse, and A. J. Smits. 1981. "Measles Vaccination and Child Mortality." *Lancet* 2:93.

Aaby, Peter, T. G. Jensen, H. L. Hansen, Hans Kristiansen, Jesper Tharup, Anja Poulsen, Morten Sodemann, Marianne Jakobsen, Kim Knudsen, M. C. da Silva, Hilton Whittle. 1988. "Trial of High-Dose Edmonston-Zagreb Measles Vaccine in Guinea-Bissau: Protective Efficacy." *Lancet* 2:809–14.

Aaby, Peter, and J. Leeuwenburg. 1988. "Patterns of Transmission and Severity of Measles Infection: A Reanalysis of Data from the Machakos Area." *Kenya Journal of Infectious Disease* 161:171–74.

Aaby, Peter, I. R. Pederson, Kim Knudsen, M. C. da Silva, C. H. Mordhorst, N. C. Helm-Petersen, B. S. Hansen, Jesper Tharup, Anja Poulsen, Morten Sodemann, Marianne Jakobsen. 1989. "Child Mortality Related to Seroconversion or Lack of Seroconversion after Measles Vaccination." *Pediatric Infectious Disease Journal* 8:197–200.

ACIP. 1989. "Measles Prevention. Recommendations of the Immunization Practices Advisory Committee." *Morbidity and Mortality Weekly Report* 38:1–18.

Anderson, R. M., and R. M. May. 1985. "Age-Related Changes in the Rate of Disease Transmission: Implications for the Design of Vaccination Programs." *Journal of Hygiene* 94:365–436.

Atkinson, W. L., and L. E. Markowitz. 1991. "Measles and Measles Vaccine." *Pediatric Infectious Disease Journal* 2:100–7.

Barclay A. J. G., A. Foster, and A. Sommer. 1987. "Vitamin A Supplements and Mortality Related to Measles: A Randomized Clinical Trail." *British Medical Journal* 294:294–96.

Barnum, H. 1989. "Evaluating Healthy Days of Life Gained from Health Projects." *Social Science and Medicine* 24:833–41.

Bart, K. S., and K. F. Lin. 1990. "Vaccine Preventable Disease and Immunization in the Developing World." *Pediatric Clinics of North America* 37: 735–56.

Bender, D., and R. J. Macauley. 1990. "Immunization Drop-Outs and Maternal Behavior: Evaluation of Reason Given and Strategies for Maintaining Gains Made in the National Vaccination Campaign in Liberia." *International Quarterly of Health Education* 9:283–88.

Bhuiya, Abbas, Bogdan Wojtyniak, Stan D'Souza, Lutfun Nahar, Kashem Skaikh. 1987. "Measles Case Fatality among the Under-Fives: A Multivariate Analysis of Risk Factors in a Rural Area of Bangladesh." *Social Science and Medicine* 24:439–43.

Black, F. L. 1982. "Measles." In Evans, A. S., ed., *Viral Infections of Humans, Epidemiology and Control*, 2d. New York: Plenum Medical Book Company.

———. 1989. "Measles Active and Passive Immunity in a Worldwide Perspective." *Prog Med Virol* 36:1–33.

Bloch, A. B., A. V. K. V. de Silva, R. L. de Sylva. "The Public Health Importance of Measles in Sri Lanka." Typescript. South-East Asia Regional Office, WHO, New Delhi, India.

Bloch, A. B., W. A. Orenstein, W. M. Ewing, W. H. Spain, G. F. Mallison, D. L. Herrmann, A. R. Hinman. 1985. "Measles Outbreak in a Pediatric Practice: Airborne Transmission in an Office Setting." *Pediatrics* 75:676–83.

Boerma, J. T., A. E. Sommerfelt, S. O. Rutsein, and G. Rojas. 1990. "Immunization: Levels, Trends and Differentials." Institute for Resource Development, Columbia, Md.

Borgono, J. M. 1983. "Current Impact on Measles in Latin America." *Review of Infectious Diseases* 5:417–21.

Boyd, D. 1991. "Computerized EPI Information Systems (CEIS)." Resources for Child Health, Arlington, Va.

Brenzel, Logan. 1990. "The Cost of EPI: A Review of Cost and Cost-Effectiveness Studies (1979–1987)." Resources for Child Health, Arlington, Va.

———. 1991. "Cost and Financing of EPI." Resources for Child Health, Arlington, Va.

Brenzel, L., and P. Claquin. 1991. "Immunization Programs and Their Costs." *World Bank Health Sector Priorities Review* HSPR-04. Washington, D.C.

Bryce, J. W., F. T. Cutts, and S. Saba. 1990. "Mass Immunization Campaigns and Quality of Immunization Services." *Lancet* 1:739–40.

Cardenas-Ayala, V. M., C. Sanchez-Vargas. 1989. "Estimation de la razón beneficio/costo de la vacunación contra el sarampión." *Salud Publica México* 31:735–44.

CCCD (Centers for Disease Control). 1990. *African Child Survival Initiative—Combatting Childhood Communicable Diseases, 1989–1990. Annual Report.* Atlanta, Ga.

Chand, Phool, R. N. Rai, Umwa Chawla, K. C. Tripathi, K. K. Datta. 1989. "Epidemiology of Measles—A Thirteen Year Prospective Study in a Village." *Journal of Communicable Disease* 21:190–99.

Chen, R. 1990. "Measles in Muyinga Health Sector, Burundi, 1989–1990." Field report. Centers for Disease Control, Atlanta, Ga.

Claquin, P. 1991. "Urban EPI." Resources for Child Health. Arlington, Va.

Clemens, J. D., Bonita F. Stanton, J. Chakraborty, Shahriar Chowdhury, M. R. Rao, Mohammed Ali, Susan Zimicki, Bogdan Wojtnyiak. 1988. "Measles Vaccination and Childhood Mortality in Rural Bangladesh." *American Journal of Epidemiology* 128:1330–39.

Clements, C. J., J. B. Milstein, Mark Grabowsky, and J. Gibson. 1988. "Research into Alternative Measles Vaccines in the 1990's." Working paper EPI/GEN/88.11. EPI Global Advisory Group. WHO/EPI, Geneva.

Coetzee, N., D. S. Berry, and M. E. Jacobs. 1991. "Measles Control in an Urbanizing Environment." *South African Medical Journal* 79:440–44.

Cotton, M. F., F. E. Berkowitz, Z. Berkowitz, P. J. Becker, and C. Heney. 1989. "Nosocomial Infections in Black South African Children." *Pediatric Infectious Disease Journal* 8:676–83.

Cutts, F. T. 1990. *Measles Control in the 1990s: Principles for the Next Decade.* Geneva: World Health Organization.

———. 1991. "Strategies to Improve Immunization Services in Urban Africa." *Bulletin of the World Health Organization* 69:407–14.

Cutts, F. T., D. C. Glik, A. Gordon, K. A. Parker, S. Diallo, F. Haba, and R. Stone. 1990. "Application of Multiple Methods to Study the Immunization Programme in an Urban Area of Guinea." *Bulletin of the World Health Organization* 68:769–76.

Cutts, F. T., R. H. Henderson, C. J. Clements, R. T. Chen, P. A. Patriarca. 1991. "Principles of Measles Control." *Bulletin of the World Health Organization* 69:1–7.

Cutts, F. T., Kortbeeks, R. Malalane, P. Penicele, K. Gingell. 1988. "The Development of Appropriate Strategies for EPI: A Case Study from Mozambique." *Health Policy and Planning* 3:291–301.

Dabis, F., A. R. Sow, R. J. Waldman, P. Bikakouri, J. Senga, G. Madzou, and T. S. Jones. 1988. "The Epidemiology of Measles in a Partially Vaccinated Population in an African City: Implications for Immunization Programs." *American Journal of Epidemiology* 127:171–78.

Davis, R. M. 1991. "Revised Measles Agenda for the 1990s: From Control to Pre-eradication." *International Child Health II* 3:45–50.

Davis, R. M., E. D. Whitman, W. A. Orenstein, S. R. Preblud, L. E. Markowitz, and A. R. Hinman. 1987. "A Persistent Outbreak of Measles Despite Appropriate Control Measures." *American Journal of Epidemiology* 126:438–49.

Dietz, K. 1976. "The Incidence of Infectious Diseases under the Influence of Seasonal Fluctuations." *Lecture Notes in Biomathematics* 11:1–15.

Dossetor, J., H. C. Whittle, and B. M. Greenwood. 1977. "Persistent Measles Infection in Malnourished Children." *British Medical Journal* 1:1633–35.

Drinkwater, H. 1885. *Remarks upon the Epidemic of Measles Prevalent in Sunderland.* Edinburgh: James Thin.

Duflo, B., H. Balique, P. Ranque, A. N. Diallo, G. Brucker, H. Alavi, and N. Prescott. 1986. "Estimation de l'impact des principales maladies en zone rurale malienne." *Revue d'Epidémiologie et de Santé Publique* 34:405–18.

Edmonson, M. B., D. G. Addiss, J. T. McPherson, J. L. Berg, S. R. Circo, and J. P. Davis. 1990. "Mild Measles and Secondary Vaccine Failure during a Sustained Outbreak in a Highly Vaccinated Population." *JAMA* 263:2467–71.

Ekunwe, E. O. 1984. "Expanding Immunization Coverage through Improved Clinic Procedures." *World Health Forum* 5:361–63.

Ellison, J. B. 1932. "Intensive Vitamin Therapy in Measles." *British Medical Journal* 2:708–11.

Enders, J. F., and T. C. Peebles. 1954. "Propagation in Tissue Cultures of Cytopathogenic Agents from Patients with Measles." *Proceedings of the Society for Experimental Biology* 86:277–86.

Fagbule, D., and F. Orifunmishe. 1988. "Measles and Childhood Mortality in Semi-urban Nigeria." *African Journal of Medical Science* 17:181–85.

Feachem, R. G., and M. A. Koblinsky. 1983. "Interventions for the Control of Diarrhoeal Diseases among Young Children: Measles Immunization." *Bulletin of the World Health Organization* 61:641–52.

Fine, P. E. M., and J. A. Clarkson. 1982a. "Measles in England and Wales—I: An Analysis of Factors Underlying Seasonal Patterns." *International Journal of Epidemiology* 11:5–14.

———. 1982b. "Measles in England and Wales—II: The Impact of Vaccination Programmes on the Distribution of Immunity in the Population." *International Journal of Epidemiology* 11:15–25.

Foege, W. H. 1984. "Banishing Measles from the World." *World Health Forum* 5:63–65.

Foege, W. H., and S. O. Foster. 1974. "Multiple Antigen Vaccine Strategies in Developing Countries." *American Journal of Tropical Medicine and Hygiene* 23:685–89.

Forgy, L., K. McInnes, S. Heinig, and B. Michaels. 1990. *Projected Costs of the Talloires Targets.* Abt and Associates. Washington, D.C.

Foster, A., and G. J. Johnson. 1988. "Measles, Corneal Ulceration, and Childhood Blindness: Prevention and Treatment." *Tropical Doctor* 18:74–78.

Foster, S. O. 1989. UNICEF/EPI consultation, Sultanate of Oman.

Foster, S. O., J. Shepperd, J. H. Davis, and A. N. Agle. 1990. "Working with African Nations to Improve the Health of Their Children." *JAMA* 263: 3303–5.

Foulon, G., M. L. Klein-Zabban, L. Gnansov-Nezzi, and G. Martin-Bouyer. 1983. "Preventing the Spread of Measles in Children's Clinics." *Lancet* 2:1498–99.

Gao, J. P., and M. D. Malison. 1988. "The Epidemiology of a Measles Outbreak on a Remote Offshore Island near Taiwan." *International Journal of Epidemiology* 17:894–98.

Garenne, Michel, and Peter Aaby. 1990. "Pattern of Exposure and Measles Mortality in Senegal." *Journal of Infectious Diseases* 161:1088–94.

Garenne, Michel, and P. Cantrell. "Rougeole et mortalité au Sénégal: étude de l'impact de la vaccination effectuée à Khombole 1965–1968 sur la survie des enfants. Estimation de la mortalité du jeune enfant pour guider les actions de santé des pays en développement." Institut National de Sciences et de Recherche Médicale, Paris. 145:512–32.

Garenne, Michel, Odile Leroy, Jean-Pierre Beau, and Ibrahima Sène. 1991. "Child Mortality after High-Titre Measles Vaccines: Prospective Study in Senegal." *Lancet* 2:903–7.

Ghana Health Assessment Project Team. 1981. "A Quantitative Method of Assessing the Health Impact of Different Diseases in Less Developed Countries." *International Journal of Epidemiology* 10:73–80.

Ginsberg, G. M., and T. H. Tulchinsky. 1990. "Costs and Benefits of a Second Measles Inoculation of Children in Israel, the West Bank, and Gaza." *Journal of Epidemiology and Community Health* 44:274–80.

Gordon, J. E., A. A. Jansen, and W. Ascoli. 1965. "Measles in Rural Guatemala. *Pediatrics* 66:779–86.

Grabowsky, M. 1991. "Missed Opportunities." Resources for Child Health, Arlington, Va.

Greenwood, B. M., A. M. Greenwood, A. K. Bradley, S. Tulloch, R. Hayes, and F. S. Oldfield. 1987. "Deaths in Infancy and Early Childhood in a Well Vaccinated, Rural, West African Population." *Annals of Tropical Pediatrics* 2:91–99.

Guyer, B., and A. M. McBean. 1981. "The Epidemiology and Control of Measles in Yaoundé, Cameroon, 1968–1975." *International Journal of Epidemiology* 10:263–69.

Halsey, N. A., Reginald Boulos, Franz Mode, Jean André, Linda Bowman, R. G. Yaeger, Serge Toureau, Joh Rohde, and Carlo Boulos. 1985. "Response to Measles Vaccine in Haitian Infants 6 to 12 Months Old." *New England Journal of Medicine* 313:544–49.

Heiby, J. R. 1990. *Supervision and the Quality of Care in the Expanded Programme on Immunization*. WHO/EPI/GAG/WP. Geneva.

Hethcote, H. W. 1976. "Qualitative Analysis of Communicable Disease Models." *Mathematical Biosciences* 28:335–56.

Hirschorn, N. 1990. "Missed Opportunities for Immunization." Resources for Child Health, Arlington, Va.

Holt, E. A., Reginald Boulos, N. A. Halsey, L. M. Boulos, C. Boulos. 1990. "Child Survival in Haiti: Protective Effect of Measles Vaccination." *Pédiatrie* 85:188–94.

Hopkins, D. R., J. F. Koplan, A. R. Hinman, and J. M. Lane. 1982. "The Case for Global Measles Eradication." *Lancet* 1:1396–98.

Hussey, G. D., and M. Klein. 1990. "A Randomized Controlled Trial of Vitamin A in Children with Severe Measles." *New England Journal of Medicine* 323:160–64.

Hussey, G. D., and J. Simpson. 1991. "Nosocomial Bacterias in Measles." *Pediatric Infectious Disease Journal* 9:715–17.

Hutchins, S. S., J. Escolan, L. E. Markowitz, C. Hawkins, A. Kimbler, R. A. Morgan, S. R. Preblud, and W. A. Orenstein. 1989. "Measles Outbreaks among Unvaccinated Preschool-Aged Children: Opportunities Missed by Health Care Providers to Administer Measles Vaccine." *Pédiatrie* 83:369–74.

Imperato, P. J., and D. Traore. 1969. "Traditional Beliefs about Measles and Its Treatment among the Bambara of Mali." *Tropical and Geographic Medicine* 21:62–67.

Job, J. S., N. A. Halsey, Reginald Boulos, Elizabeth Holt, Dorothy Farrell, Paul Albrecht, J. R. Brutus, Mario Adrien, Jean André, Edward Chan, Patricia Kissinger, Carlo Boulos, and the Cité Soleil/JHU Project Team. 1991. "Successful Immunization of Infants at 6 Months of Age with High Dose Edmonston-Zagreb Measles Vaccine." *Pediatric Infectious Disease Journal* 10:303–11.

John, A. M. 1990a. "Endemic Disease in Host Populations with Fully Specified Demography." *Population Biology* 37:455–71.

———. 1990b. "Transmission and Control of Childhood Infectious Diseases: Does Demography Matter?" *Population Studies* 44:195–215.

John, A. M., and S. D. Tuljapurkar. 1990. "Childhood Infectious Diseases in LDCs: Immunization Program Design and Evaluation Using Demographic-Epidemiologic Models." Working Paper 22, Research Division, Population Council, New York.

John, T. Jacob, Abraham Joseph, T. I. George, Janaki Radhakrishnan, Rajdayal Singh, Kuryan George. 1980. "Epidemiology and Prevention of Measles in Rural South India." *International Journal of Medical Research* 72:153–58.

John, T. Jacob, M. Ray, and M. C. Steinhoff. 1984. "Control of Measles by Annual Pulse Immunization." *American Journal of Diseases of Children*: 138: 299–300.

Kalter, H. D., R. H. Gray, R. E. Black, and S. A. Gultiano. 1990. "Validation of Postmortem Interviews to Ascertain Selected Causes of Death in Children." *International Journal of Epidemiology* 19:380–86.

Kaschula, R. O., J. Druker, and A. Kipps. 1983. "Late Morphologic Consequences of Measles—A Lethal and Debilitating Lung Disease among the Poor." *Review of Infectious Diseases* 5:395–404.

Kasongo Project Team. 1981. "Influence of Measles Vaccination on Survival Pattern of 7–35 Month Old Children in Kasongo, Zaire." *Lancet* 1:764–67.

Kenyan Ministry of Health and WHO (World Health Organization). 1977. "Measles Immunity in the First Year after Birth and the Optimum Age for Vaccination in Kenyan Children." *Bulletin of the World Health Organization* 55:21–31.

Kermack, W. O., and A. G. McKendrick. 1927. "A Contribution to the Mathematical Theory of Epidemics." *Proceedings of the Royal Society of London*, series A, 115:700–21.

Killewo, Japhet, Cyprian Makwaya, Emmanuel and Rose Munubhi, and Mpembeni. 1991. "The Protective Effect of Measles Vaccine under Routine Vaccination Conditions in Dar Es Salaam, Tanzania: A Case-Control Study." *International Journal of Epidemiology* 20:508–14.

Kipps, A., and R. O. C. Kaschula. 1976. "Virus Pneumonia following Measles." *South African Medical Journal* 50:1083–88.

Klein-Zabban, M. L., G. Foulon, C. Gaudebout, J. Badoual, and J. Assi Adou. 1987. "Fréquence des rougeoles nosocomiales dans un centre de protection maternelle et infantile d'Abidjan." *Bulletin of the World Health Organization* 65:197–201.

Koenig, M. A., M. A. Khan, B. Wojtyniak, J. D. Clements, J. Chakraborty, V. Fauveau, J. F. Phillips, J. Akbar, and U. S. Barua. 1990. "Impact of Measles Vaccination on Childhood Mortality in Rural Bangladesh." *Bulletin of the World Health Organization* 68:441–47.

Koster, F. T., G. C. Curlin, K. M. A. Azia, and Azizul Haque. 1981. "Synergistic Impact of Measles and Diarrhoea on Nutrition and Mortality in Bangladesh." *Bulletin of the World Health Organization* 59:901–8.

Krober, M. S., C. E. Stracener, and J. W. Bass. 1991. "Decreased Measles Response after Measles–Mumps–Rubella Vaccine in Infants with Colds." *JAMA* 265:2095–96.

Lesotho. 1990. Measles control in Lesotho.

Loras-Duclaux, I., L. David, D. Peyramond D. Floret, A. Lachaux, and M. Hermier. 1988. "Etude épidémiologique et évaluation du coût de la rougeole dans les hôpitaux lyonnais durant cinq années." *Pédiatrie* 43:451–54.

McBean, A. M., S. O. Foster, K. L. Herrmann, and C. Gateff. 1976. "Evaluation of a Mass Measles Immunization Campaign in Yaoundé, Cameroon." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 70:206–12.

McFarland, D. A., and D. K. Kraushaar. 1990. "Cost of the EPI and CDD Programmes in Swaziland." Centers for Disease Control, Atlanta, Ga.

Maina-Ahlberg, B. 1979. "Beliefs and Practices Concerning Treatment of Measles and Acute Diarrhea among the Akamba." *Tropical and Geographic Medicine* 31:139–48.

Markowitz, L. 1990. "Measles Control in the 1990s. Immunization before 9 Months of Age." World Health Organization, Geneva.

Markowitz, L. E., and P. Nieburg. 1991. "The Burden of Acute Respiratory Infection Due to Measles in Developing Countries and the Potential Impact of Measles Vaccine." *Review of Infectious Diseases* 13:555–61.

Markowitz, L. E., N. Nzilambi, W. J. Driskell, M. G. Sension, E. Z. Rovira, P. Nieburg, and R. W. Rider. 1989. "Vitamin A Levels and Mortality among Hospitalized Measles Patients, Kinshasa, Zaire." *Journal of Tropical Pediatrics* 35:109–12.

Markowitz, L. E., and W. A. Orenstein. 1990. "Measles Vaccines." *Pediatric Clinics of North America* 37:603–25.

Markowitz, L. E., S. R. Preblud, P. E. M. Fine, and W. A. Orenstein. 1990. "Duration of Live Measles Vaccine—Induced Immunity." *Pediatric Infectious Disease Journal* 8:101–10.

Markowitz, L. E., J. Sepúlveda, J. L. Diaz-Ortega, J. L. Valdespino, P. Albrecht, E. R. Zell, J. Stewart, M. L. Zarate, and R. H. Bernier. 1990. "Immunization of Six-Month-Old Infants with Different Doses of Edmonston-Zagreb and Schwarz Measles Vaccine." *New England Journal of Medicine* 322:580–87.

Mast, Eric, J. L. Berg, L. P. Hanrahan, J. T. Wassell, and J. P. Davis. 1990. "Risk Factors for Measles in a Previously Vaccinated Population and Cost-Effectiveness of Revaccination Strategies." *JAMA* 264:2529–33.

Mathias, R. G., W. G. Meekison, T. A. Arcand, and M. T. Schechter. 1989. "The Role of Secondary Vaccine Failures in Measles Outbreaks." *American Journal of Public Health* 79:475–78.

Morley, D. 1973. "'Severe' Measles." In D. Morley, ed., *Pediatric Priorities in the Developing World*. London: Butterworth.

Mosely, W. H., and L. C. Chen. 1984. "An Analytic Framework for the Study of Child Survival in Developing Countries." In *Child Survival Strategies for Research*. Supp. *Population and Development Review* 10S:25–45.

Narain, J. P., S. Khare, S. R. S. Rana, and K. B. Banerjee. 1989. "Epidemic Measles in an Isolated, Unvaccinated Population, India." *International Journal of Epidemiology* 18:952–58.

Nokes, D. J., A. R. McLean, R. M. Anderson, and M. Grabowsky. 1990. "Measles Immunization Strategies for Countries with High Transmission Rates: Interim Guidelines Predicted Using a Mathematical Model." *International Journal of Epidemiology* 19:703–10.

Orenstein, W. A., R. H. Bernier, T. J. Dondero, A. R. Hinman, J. S. Marks, K. J. Bart, and B. Sirotkin. 1985. "Field Evaluation of Vaccine Efficacy." *Bulletin of the World Health Organization* 63:1055–68.

Orenstein, W. A., L. Markowitz, S. R. Preblud, A. R. Hinman, A. Tomasi, and K. J. Bart. 1986. "Appropriate Age for Measles Vaccination in the United States." *Developments in Biological Standards* 65:13–21.

PAHO (Pan-American Health Organization). 1990. "Plan to Eliminate Indigenous Transmission of Measles in the English Speaking Caribbean." *Bulletin of the Pan-American Health Organization* 24:240–46.

Panum, P. L. 1939. "Observations Made during the Epidemic of Measles on the Faroe Islands in the Year 1846." *Medical Classics* 3:839–86.

Phillips, M. A., R. G. Feachem, and A. Mills. 1987. *Options for Diarrhoea Control*. EPC Publication 13. London: School of Hygiene and Tropical Medicine.

Pison, G., and N. Bonneuil. 1988. "Increased Risk of Measles Mortality for Children with Siblings among the Fula Bande, Senegal." *Review of Infectious Diseases* 10:468–70.

Ponninghaus, J. M. 1980. "The Cost/Benefit of Measles Immunization: A Study from Southern Zambia." *Journal of Tropical Medicine and Hygiene* 83:141–49.

Preblud, S. R., and S. L. Katz. 1988. "Measles Vaccine." In S. A. Plotkin and E. A. Mortimer, eds., *Vaccines*. Philadelphia: W. B. Saunders.

Prescott, N., A. Prost, and R. Le Berre. 1984. "The Economics of Blindness Prevention in Upper Volta under the Onchocerciasis Control Program." *Social Science and Medicine* 19:1051–55.

de Quadros, C. A., J. K. Andrus, J. M. Olive, C. M. da Silveria, R. E. Eikhof, Peter Carrasco, J. W. Fitzsimmon, and Francisco P. Pinheiro. 1991. "Eradication of Poliomyelitis: Progress in the Americas." *Pediatric Infectious Disease Journal* 10:222–29.

Rahmathullah, Laxmi, B. A. Underwood, R. D. Thulesiraj, R. C. Milton, Kala Ramaswamy, Raheem Rahmathullah, Geneesh Babu, and B. Com. 1990. "Reduced Mortality among Children in Southern India Receiving a Small Weekly Dose of Vitamin A." *New England Journal of Medicine* 323:929–35.

Robertson, R. L. 1985. *Cost of the CCCD Project in Swaziland, 1984–1985*. University Research Corporation.

Robertson, R. L., S. O. Foster, H. F. Hull, and P. J. Williams. 1987. "Cost-Effectiveness of Immunization in The Gambia." *Journal of Tropical Medicine and Hygiene* 88:343–51.

Rosenthal, G. 1990. "Sustainability of EPI." Resources for Child Health, Arlington, Va.

Roungou, J. B. 1991. Coverage Survey, Central African Republic.

Sabin, A. B., A. Flores Arechiga, J. Fernandez de Castro, J. L. Sever, D. L. Madden, I. Shekarchi, P. Albrecht. 1983. "Successful Immunization of Children with and without Maternal Antibody by Aerosolized Measles Vaccine." *JAMA* 249:2651–52.

Sahuguede, P., A. Roisin, I. Sanou, B. Nacro, F. Talls. 1989. "Epidémie de rougeole au Burkina Faso: 714 cas hospitalisés à l'hôspital de Bobo-Dioulasso." *Annals of Pediatrics* 36:244–51.

Schenzle, D. 1989. "An Age-Structured Model of Pre- and Post-vaccination Measles Transmission." IMA *(International Mathematics Association) Journal of Mathematics Applied to Medicine and Biology* 1:16–91.

Shears, P., A. M. Berry, R. Murphy, and M. A. Nabil. 1987. "Epidemiologic Assessment of the Health and Nutrition of Ethiopian Refugees in Emergency Camps in Sudan." *British Medical Journal* 295:314–18.

Shepard, D. S., L. Sanoh, and E. Coffi. 1986. "Cost-Effectiveness of the Expanded Programme on Immunization in the Ivory Coast: A Preliminary Assessment." *Social Science and Medicine* 22:369–77.

Smith, E. A., and S. O. Foster. 1970. "The Effect of the Smallpox Eradication Measles Control Programme on Measles Admissions to the Lagos Infectious Disease Hospital, Yaba, Nigeria." *West African Medical Journal* 19:51–56.

Sommer, A. 1990. "Vitamin A Status, Resistance to Infection, and Childhood Mortality." *Annals of the New York Academy of Science* 587:17–23.

Taylor, W. R., Ruti-Kalisa, Mambu Ma-Disu, and J. M. Weinman. 1988. "Measles Control Efforts in Urban Africa Complicated by High Incidence of Measles in the First Year of Life." *American Journal of Epidemiology* 127:788–94.

Toole, M. J., R. W. Steketee, R. J. Waldman, and P. Nieburg. 1989. "Measles Prevention and Control in Emergency Settings." *Bulletin of the World Health Organization* 67:381–88.

Toole, M. J., and R. J. Waldman. 1988. "An Analysis of Mortality among Refugee Populations in Thailand, Somalia, and Sudan." *Bulletin of the World Health Organization* 66:237–47.

Tuljapurkar, S. D., and A. M. John. 1991. "Disease in Changing Populations: Growth and Disequilibrium." *Population Biology* 40:322-53.

UNICEF. 1990. *Universal Child Immunization Reaching the Urban Poor*. Urban Examples 16. New York.

United States, National Vaccine Advisory Committee. 1991. The Measles Epidemic: The Problems, Barriers, Recommendations.

Verduzco, E., C. Calderon, and E. Velazquez-Franco. 1974. "Repercusiones de la vacunación contra el sarampión en México." *Salud Pública México* 16: 707–20.

Voorhoeve, A. M., A. S. Muller, T. W. Schulpen, W. Gemert, H. A. Valkenburg, and H. E. Ensering. 1977. "Agents Affecting Health of Mother and Child in a Rural Area of Kenya. III: The Epidemiology of Measles." *Tropical and Geographic Medicine* 29:428–40.

Walsh, J. A. 1983. "Selective Primary Health Care: Strategies for Control of Disease in the Developing World. IV: Measles." *Review of Infectious Diseases* 5:330–40.

Weierbach, R. 1989. "Rapport de mission au Rwanda du Juillet au 4 Août." Centers for Disease Control, Atlanta, Ga.

White, C. C., J. P. Koplan, and W. A. Orenstein. 1985. "Benefits, Risks, and Costs of Immunization for Measles, Mumps, and Rubella." *American Journal of Public Health* 75:739–44.

Whittle, H. C., A. Bradley-Moore, A. Fleming, and B. M. Greenwood. 1973. "Effects of Measles and the Immune Response of Nigerian Children." *Archives of Diseases of Children* 48:753–56.

Whittle, H. C., M. G. M. Rowland, G. F. Mann, W. H. Lamb, and R. A. Lewis. 1984. "Immunization of 4–6 Month Old Gambian Children with Edmonston-Zagreb Measles Vaccine." *Lancet* 2:834–37.

WHO (World Health Organization). 1988. *Expanded Programme on Immunization Mid-Level Managers Module: Measuring Vaccination Coverage*. Geneva.

———. 1989a. "High Dose EZ Measles Vaccine." EPI/GAG/89/WP13. Geneva.

———. 1989b. "Vitamin A Update." EPI/GAG/89/WP13. Geneva.

———. 1991. "Plan of Action for Global Measles Control." EPI/GAG/91/WP12. Geneva.

———. 1992. "Using Immunization Contacts to Combat Vitamin A Deficiency." EPI/GAG/92.

WHO/EPI (World Health Organization/Expanded Programme on Immunization). 1984. "Expanded Programme on Immunization, Indications and Contraindications for Vaccines Used in the EPI." WHO/WER (*Weekly Epidemological Record) 59:13–16*.

———. 1985. "Expanded Programme on Immunization, Public Health Importance of Measles." WHO/WER 60:103–5. Burma.

———. 1979. "Expanded Programme on Immunization, Measles Immunization." WHO/WER 54:337–39. Kenya.

———. 1986. "Expanded Programme on Immunization, Measles Vaccine Efficacy." WHO/WER 61:356–57. Poland.

———. 1985. "Public Health Importance of Measles." WHO/WER 60:95–97. Sri Lanka.

———. 1989. "Expanded Programme on Immunization, Missed Opportunities for Immunization." WHO/WER 64:32–34. Zimbabwe.

WHO/UNICEF (World Health Organization/United Nations Children's Fund). 1985. *Planning Principles for Accelerated Immunization Strategies. A Joint WHO/UNICEF Statement*. Geneva.

Yach, D., C. Metcalf, P. Lachman, G. Hussey, E. Subotsky, R. Blignaut, A. J. Flisher, H. S. Schaaf, and N. Cameron. 1991. "Missed Opportunities for Measles Immunization in Selected Western Cape Hospitals." *South African Medical Journal* 79:437–39.